Liver Digest

A weekly update of PLRC happenings

October 24, 2019

www.livercenter.pitt.edu

Featured Faculty - Dr. Jianhua Luo

In this issue

Next Week's Seminar

PLRC Chronic Liver Injury - Special Interest Group

Tues., 10/29/2019

12:00 to 1:00 p.m.

Berkman Boardroom (7th Floor Montefiore)

Biliary Injury and Repair

Dr. James Squires - Clinician

Dr. Donghun Shin - Basic Scientist

Pizza will be provided.

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

Upcoming Conferences

Center for Pharmacogenetics Symposium

Wednesday 11/13/2019

University Club, Ballroom A

"Twenty-Year Journey University of Pittsburgh School of Pharmacy Center for Pharmacogenetics From Pharmacogenetics to Molecular Medicine and Pharmaceutics"

For program, please **click here**.

To register, please follow the link: **https://www.alumnionline.pitt.edu/s/1729/2-pittsburgh/interior.aspx?sid=1729&gid=2&pgid=3528&content_id=4421**

The registration and meals are free.

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:

Berardi, G., Morise, Z., Sposito, C., Igarashi, K., Panetta, V., Simonelli, I., Kim, S., Goh, Brian K.P., Kubo, S., Tanaka, S., Takeda, Y., Ettorre, G.M., Wilson, G.C., Cimino, M., Chan, C-Y., Torzilli, G., Cheung,T.T., Kaneko, H., Mazzaferro, V., **Geller, D.A.**, Han, H-S., Kanazawa, A., Wakabayashi, G., Troisi, R.I.,Development of a nomogram to predict outcome after liver resection for hepatocellular carcinoma in child-pugh bcirrhosis, Journal of Hepatology (2019).

ABSTRACT

BACKGROUND & AIMS: Treatment allocation of patients with hepatocellular carcinoma (HCC) on Child-Pugh B (CP-B) cirrhosis is controversial. Liver resection has been proposed by small series with acceptable outcomes, but data are limited. The aim of this study was to evaluate the outcomes of patients undergoing liver resection for HCC in CP-B cirrhosis focusing on the surgical risks and survivals.

METHODS: Patients were retrospectively pooled from 14 international referral centers from 2002 to 2017. Postoperative and oncological outcomes were investigated. Prediction models for surgical risks and survivals were constructed.

RESULTS: 253 patients were included. 57.3% of patients had a preoperative platelet count <100.000/mm3, 43.5% had preoperative ascites, and 56.9% had portal hypertension. A minor hepatectomy was most commonly performed (84.6%) and 122 (48.2%) were operated on by minimally invasive surgery (MIS). 90 days

mortality was 4.3% with six patients (2.3%) dying from liver failure. 108 patients (42.7%) experienced complications of which the most common was ascites (37.5%). Patients undergoing major hepatectomies had higher 90 days mortality (10.3% vs. 3.3%; p=0.04) and morbidity rate (69.2% vs. 37.9%; p<0.001). Patients undergoing an open hepatectomy had higher morbidity (52.7% vs. 31.9%; p=0.001) compared to MIS. A prediction model for surgical risk was constructed (**https://childb.shinyapps.io/morbidity/**). The 5-year overall survival (OS) rate was 47%, and 56.9% of patients experienced recurrence. Prediction models for OS (**https://childb.shinyapps.io/survival/**) and disease-free survival (**https://childb.shinyapps.io/DFsurvival/**) were constructed.

CONCLUSIONS: Liver resection for HCC in CP-B cirrhosis should be considered after careful selection according to patients' characteristics, tumor pattern and liver function as well as minimizing surgical stress. An estimation of the surgical risk and survival advantage may be helpful in treatment allocation eventually improving postoperative morbidity achieving safe oncological outcomes.

LAY SUMMARY: Liver resection for hepatocellular carcinoma in advanced cirrhosis (Child-Pugh B score) is associated with a high rate of postoperative complications. However, due to the limited therapeutic alternatives in this setting, recent studies have shown promising results after accurate patients' selection. In our international multicenter study we provide three clinical models to predict postoperative surgical risks and long-term survivals following liver resection to help in treatment allocation eventually improving the outcomes.

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

Review Article:

Dhawan A, Lawlor MW, Mazariegos GV, **McKiernan P, Squires JE**, Strauss KA, Gupta D, James E, Prasad S. Disease burden of Crigler-Najjar syndrome: systematic review and future perspectives. J Gastroenterol Hepatol. 2019 Sep 8. doi: 10.1111/jgh.14853. PubMed PMID: 31495946.

ABSTRACT

BACKGROUND AND AIM: Crigler-Najjar syndrome (CNS) results from biallelic mutations of UGT1A1 causing partial or total loss of uridine 5´-diphosphate glucuronyltransferase activity leading to unconjugated hyperbilirubinemia and

its attendant risk for irreversible neurological injury (kernicterus). CNS is exceedingly rare and has been only partially characterized through relatively small studies, each comprising between two and 57 patients.

METHODS: We conducted a systematic literature review to consolidate data on the patient, caregiver, and societal burden of CNS.

RESULTS: We identified 28 articles on clinical aspects of CNS, but found no published data on its humanistic or economic burden. In patients with complete UGT1A1 deficiency (type 1 CNS [CNS-I]), unconjugated bilirubin levels increase 3-6 mg/dL per day during the newborn period and reach neurologically dangerous levels between 5 and 14 days of age. Phototherapy is the mainstay of treatment, but poses significant challenges to patients and their families. Despite consistent phototherapy, patients with CNS-I have worsening hyperbilirubinemia with advancing age. Liver transplantation is the only definitive therapy for CNS-I and is increasingly associated with excellent long-term survival, but also incurs high costs, medical and surgical morbidities, and risks of immunosuppression.

CONCLUSIONS: CNS is associated with a substantial burden, even with existing standards of care. The development of novel disease-modifying therapies has the potential to reduce disease burden and improve the lives of CNS patients and their families.

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

Original Article:

Gong Z, Zhang X, Su K, Jiang R, Sun Z, Chen W, Forno E, **Goetzman ES**, Wang J, **Dong HH**, Dutta P, Muzumdar R. Deficiency in AIM2 induces inflammation and adipogenesis in white adipose tissue leading to obesity and insulin resistance. Diabetologia. 2019 Sep 11. doi: 10.1007/s00125-019-04983-x. PubMed PMID: 31511929.

ABSTRACT

AIMS/HYPOTHESIS:

Absent in melanoma 2 (AIM2) is a cytosolic sensor for double-stranded DNA and a tumour suppressor. Binding of double-stranded DNA to AIM2 forms the AIM2 inflammasome, leading to activation of caspase-1 and production of IL-1β and IL-18. Although inflammasome-independent effects of AIM2 have been reported,

its role in energy metabolism is unknown. We aimed to evaluate the effect of AIM2 in energy metabolism and glucose homeostasis.

METHODS:
Male and female whole body Aim2 knockout (Aim2-/-) mice were used in the current study. Body weight, food intake, body composition, energy expenditure, fasting blood glucose levels, GTT and body temperature were measured at indicated time points. RNA sequencing was carried out on gonadal white adipose tissue (gWAT) in 14-month-old female mice. mRNA and protein levels in tissues were analysed by quantitative real-time PCR and immunoblot. Immune cell infiltration in gWAT was examined by flow cytometry. Stromal vascular fractions isolated from gWAT were used to investigate adipocyte differentiation.

RESULTS:
Male and female Aim2-/- mice were obese compared with wild-type controls from 7 weeks of age until 51 weeks of age, with increased adiposity in both subcutaneous and visceral fat depots. While there were no differences in food intake, Aim2-/- mice demonstrated decreased energy expenditure and impaired brown adipose tissue function compared with wild-type controls. Fasting glucose and insulin levels were elevated, and Aim2-/- mice were glucose intolerant on intraperitoneal GTT. RNA sequencing revealed marked upregulation of the IFN-inducible gene Ifi202b, which encodes protein 202 (p202) and elevated inflammatory signalling in gWAT of Aim2-/- mice. Increased infiltration of total and Ly6Clow monocytes was noted at 8 weeks of age in gWAT, before the onset of obesity and insulin resistance. Ifi202b knockdown blocked adipogenesis in stromal vascular fractions and reduced inflammation in bone marrow-derived macrophages, demonstrating a key role of p202 in mediating the increased adipogenesis and inflammation in Aim2-/- mice.

CONCLUSIONS/INTERPRETATION:
These results demonstrate a fundamental role for AIM2 in energy metabolism, inflammation and insulin resistance. Our studies establish a novel link between the innate immunity proteins, AIM2 and p202, and metabolism.

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

Original Article:
Yazdani HO, Roy E, Comerci AJ, van der Windt DJ, Zhang H, Huang H, Loughran P,

Shiva S, **Geller DA**, Bartlett DL, Tsung A, Sheng T, Simmons RL, Tohme S. Neutrophil Extracellular Traps Drive Mitochondrial Homeostasis in Tumors to Augment Growth. Cancer Res. 2019 Sep 13. pii: canres.0800.2019. doi: 10.1158/0008-5472.CAN-19-0800. PubMed PMID: G50.

ABSTRACT
Neutrophil infiltration and neutrophil extracellular traps (NETs) in solid cancers are associated with poorer prognosis but the mechanisms are incompletely understood. We hypothesized that NETs enhance mitochondrial function in tumor cells providing extra energy for accelerated growth. Metastatic colorectal cancer tissue showed increased intratumoral NETs and supranormal preoperative serum MPO-DNA, a NET marker. Higher MPO-DNA correlated with shorter survival. In mice, subcutaneous tumor implants and hepatic metastases grew slowly in PAD4-KO mice, genetically incapable of NETosis. In parallel experiments, human cancer cell lines grew slower in nu/nu mice treated with DNAse, which disassembles NETs. PAD4-KO tumors manifested decreased proliferation, increased apoptosis and increased evidence of oxidative stress. PAD4-KO tumors had decreased mitochondrial density, mitochondrial DNA, a lesser degree of ATP production, along with significantly decreased mitochondrial biogenesis proteins PGC-1α, TFAM and NRF-1. In vitro, cancer cells treated with NETs upregulated mitochondrial biogenesis associated genes, increased mitochondrial density, increased ATP production, enhanced the percentage of cancer cells with reduced mitochondrial membrane potential and increased the oxygen consumption rate. Furthermore, NETs increased cancer cell's expression of fission and fusion associated proteins, DRP-1 and MFN-2, and mitophagy-linked proteins, PINK1 and Parkin. All of which were decreased in PAD4-KO tumors. Mechanistically, neutrophil elastase (NE) released from NETs activated TLR-4 on cancer cells leading to PGC-1α upregulation, increased mitochondrial biogenesis and accelerated growth. Taken together, NETs can directly alter the metabolic programming of cancer cells to increase tumor growth. NETs represent a promising therapeutic target to halt cancer progression.

To access full text, please **click here**.

Review Article:

Thomas G, Horwich A. Chemical Strike against a Dominant-Inherited MUC1-Frameshifted Protein Associated with Progressive Kidney Disease. Trends Mol Med. 2019 Sep 11. pii: S1471-4914(19)30234-5. doi:

10.1016/j.molmed.2019.08.011. PubMed PMID: 31521560.

ABSTRACT
In a recent paper by Dvela-Levitt et al., chemical screening using an immunofluorescent assay identified a compound that caused removal of a dominant-inherited misfolded secretory protein, mucin1-frameshifted, from an intracellular location in immortalized renal epithelial cells of a patient affected with progressive medullary cystic kidney disease. This illustrates the power of chemical screening at the cellular level to address specific proteinopathies and the utility of such compounds to illuminate novel cellular pathways that can clear toxic proteins.

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

Employment Opportunity

Novartis Institutes for BioMedical Research / Disease Area x
Research Investigator, Liver Diseases
Job announcement is **available here**.

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