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Liver Digest

A weekly update of PLRC happenings

November 21, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Silvia Liu

In this issue

Spring 2020 Seminars and Enrichment

Jan 7	PLRC SIG	Dr. Michael Nalesnik & Dr. Silvia Liu
Jan 28	PLRC Seminar	Dr. Suthat Liangpunsakul (Indiana University School of Medicine)
Mon, Feb 3	Grant-writing workshop	PLRC P&F Awardees' presentations and grant-writing workshop
Feb 18	PLRC Seminar	Dr. David Mangelsdorf (UT Southwestern Medical Center)
Mar 11	PLRC Co-sponsored seminar	Dr. Nicolas LaRusso (Mayo Clinic)
Mar 24	PLRC Seminar	Dr. Ekihiro Seki (Cedars Sinai)
Apr 21	PLRC Seminar	Dr. Harmeet Malhi (Mayo Clinic)
May 5	PLRC SIG	Dr. Andres Duarte-Rojo & Dr. Dean Yimlamai
June 2	PLRC SIG	Dr. Jaideep Behari & Dr. Juliane Beier
June 23	PLRC Seminar	Dr. Daniela Sia (Icahn School of Medicine at Mount Sinai)

Details for each event will be posted on **https://www.livercenter.pitt.edu/events** as they become available.

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:

Francipane MG, Han B, **Lagasse E**. Host Lymphotoxin-β Receptor Signaling Is Crucial for Angiogenesis of Metanephric Tissue Transplanted into Lymphoid Sites. Am J Pathol. 2019 Oct 1. pii: S0002-9440(19)30750-3. doi: 10.1016/j.ajpath.2019.08.018. PubMed PMID: 31585070.

ABSTRACT

The mouse lymph node (LN) can provide a niche to grow metanephric kidney to maturity. Here, we show that signaling through the lymphotoxin-β receptor (LTβR) is critical for kidney organogenesis both in the LN and the omentum. By transplanting kidney rudiments either in the LNs of mice undergoing LTβR antagonist treatment or in the omenta of LTBR knockout (LTβR-/-) mice, the host LTβR signals were found to be crucial for obtaining a well-vascularized kidney graft. Indeed, defective LTβR signaling correlated with decreased expression of endothelial and angiogenic markers in kidney grafts as well as structural alterations. Because the number of glomerular endothelial cells expressing the LTβR target nuclear factor κB-inducing kinase (NIK) decreased in the absence of a functional LTβR, it was speculated that an LTβR/NIK axis mediated the angiogenetic signals required for successful ectopic kidney organogenesis, given the established role of NIK in neovascularization. However, the transplantation of kidney rudiments in omenta of NIK-/- mice revealed that NIK is dispensable for ectopic kidney vascular integration and maturation. Finally, defective LTβR signaling impaired compensatory glomerular adaptation to renal mass reduction, indicating that kidney regeneration approaches, besides whole kidney reconstruction, might benefit from the presence of LTβR signals.

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

Commentary:

Zhao Q, **Miljkovic I**. Weight Loss and Blood Pressure Changes, Roles Played by Genetic Susceptibility and Macronutrients. Hypertension. 2019 Oct 28:HYPERTENSIONAHA11913677. doi: 10.1161/HYPERTENSIONAHA.119.13677. PubMed PMID: 31656100.

This article is a commentary on the manuscript:
Dianjianyi Sun, Tao Zhou, Xiang Li, Yoriko Heianza, Zhaoxia Liang, George A. Bray, Frank M. Sacks, Lu Qi. Genetic Susceptibility, Dietary Protein Intake, and Changes of Blood Pressure: The POUNDS Lost Trial. Originally published28 Oct 2019 **https://doi.org/10.1161/HYPERTENSIONAHA.119.13510** Hypertension. 2019;74:1460–1467

For full text of Dr. Miljkovic's commentary, please **click here**.

For full text of D Sun et al's article, please **click here**.

Original Article:

Santanasto AJ, **Miljkovic I**, Cvejkus RK, Wheeler VW, Zmuda JM. Sarcopenia Characteristics are associated with Incident Mobility Limitations in African Caribbean Men: The Tobago Longitudinal Study of Aging. J Gerontol A Biol Sci Med Sci. 2019 Oct 8. pii: glz233. doi: 10.1093/gerona/glz233. PubMed PMID: 31593581.

ABSTRACT

BACKGROUND: Sarcopenia varies by ethnicity, and has a major impact on health in older adults. However, little is known about sarcopenia characteristics in African ancestry populations outside the United States. We examined sarcopenia characteristics in 2,142

African Caribbean men aged 59.0±10.4 years (range: 40-92 years) in Tobago, and their association with incident mobility limitations in those aged 55+ (n=738).

METHODS: BMI, grip strength, DXA (dual-x-ray absorptiometry) appendicular lean mass (ALM) and self-reported mobility limitations were measured at baseline, and six-years later. Change in sarcopenia characteristics, including grip strength, grip strength/BMI, ALMBMI and ALM/ht2, were determined. Foundations for the National Institutes of Health Sarcopenia Project (FNIH) and European Working Group for Sarcopenia in Older People 2 (EWGSOP2) cut-points were also examined. Odds ratios (OR) and 95% confidence intervals (CI) for mobility limitation were calculated using multivariable linear regression models adjusted for covariates.

RESULTS: Overall, sarcopenia prevalence was quite low using the FNIH (0.3%) and EWGSOP2 (0.6%) operational cut-points, but was higher in those aged 75+ (2.1% [FNIH] and 3.7% [EWGSOP2]). Prevalence was also higher when based on "weakness", vs. "low ALM". When sarcopenia markers were examined separately, baseline levels, but not changes, were associated with incident mobility limitations. Baseline grip strength/BMI was a particularly strong risk factor for incident mobility limitations (OR per SD: 0.50; 95% CI: 0.37-0.68).

CONCLUSIONS: Our findings suggest that grip strength normalized to body mass, measured at one time-point, may be a particularly useful phenotype for identifying African Caribbean men at risk for future mobility limitations.

Original Article:

Zhang W, Meyfeldt J, Wang H, Kulkarni S, Lu J, Mandel JA, Marburger B, Liu Y, Gorka JE, **Ranganathan S, Prochownik EV**. β-Catenin mutations as determinants of hepatoblastoma phenotypes in mice. J Biol Chem. 2019 Oct 9. pii: jbc.RA119.009979. doi: 10.1074/jbc.RA119.009979. PubMed PMID: 31597698.

ABSTRACT

Hepatoblastoma (HB) is the most common pediatric liver cancer. Although long-term survival of HB is generally favorable, it depends on clinical stage, tumor histology, and a variety of biochemical and molecular features. HB appears almost exclusively before the age of 3 years, is represented by seven histological subtypes, and is usually associated with highly heterogeneous somatic mutations in the catenin β1 (CTNNB1) gene, which encodes β-catenin, a Wnt ligand-responsive transcriptional co-factor. Numerous recurring β-catenin mutations, not previously documented in HB, have also been identified in various other pediatric and adult cancer types. Little is known about the underlying factors that determine the above HB features and behaviors or whether non-HB-associated β-catenin mutations are tumorigenic when expressed in hepatocytes. Here, we investigated the oncogenic properties of 14 different HB- and non-HB-associated β-catenin mutants encoded by Sleeping Beauty vectors following their delivery into the mouse liver by hydrodynamic tail-vein injection. We show that all β-catenin mutations, as well as WT β-catenin, are tumorigenic when co-expressed with a mutant form of yes-associated protein (YAP). However, tumor growth rates, histologies, nuclear-to-cytoplasmic partitioning, and metabolic and transcriptional landscapes were strongly influenced by the identities of the β-catenin mutations. These findings provide a context for understanding at the molecular level the notable biological diversity of HB.

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

PLRC at AASLD

Many PLRC members actively participated in the AASLD's The Liver Meeting® 2019. Two of the major events are highlighted below.

1. **Basic Science Symposium Highlights New Findings in Liver Regeneration.** **Dr. Michalopoulos**, chair of Pathology and Dr. Xiao-Ming Yin (a UPMC alumnus) organized a highly successful and well-attended basic research symposium. Many PLRC members were invited to give a talk in this session including Drs. Michalopoulos, Monga, Nejak-Bowen and Soto-Gutierrez. The symposium covered the timely topics of the cell-molecule circuits that are activated during liver regeneration after surgical resection and also emphasized the role of macrophages, endothelial cells and stellate cells in the process. The role of cellular reprogramming--especially how hepatocytes and cholangiocytes can served as facultative progenitors for each other to mediate hepatobiliary repair--was also discussed in great depth. Unique cellular processes including autophagy, cellular senescence and immune response as the mediators of cellular reprogramming which could assist in modulating hepatocyte differentiation and function while also providing novel models to study cellular reprogramming, were presented. Eventually, de novo organogenesis using iPS cells, decellularized livers as scaffolds to generate organoids or organs for transplantation, were discussed. Thus all important and timely concepts of hepatic regenerative medicine were discussed in the session. AASLD daily news covered the symposium, and the write up is available at **https://www.aasldnews.org/basic-science-symposium-highlights-new-findings-in-liver-regeneration/**

2. **Basic research debrief at AASLD 2019.** With over 900 abstracts presented, AASLD was a successful platform for disseminating and

discussing basic research in liver. **Dr. Gavin Arteel**, provided a debrief of these sessions at a highly-attended session at the meeting. The debrief, which is available at the website below, highlighted the state of the art in basic sciences presented by many groups including PLRC members. **https://www.aasldnews.org/debrief-reviews-high-impact-basic-science-presented-at-the-liver-meeting/**

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