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Liver Digest

A weekly update of PLRC happenings

December 19, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Hun-Way Hwang

In this issue

Happy Holidays

Due to the holidays, the Liver Digest will not be published on Thursday, December 26. Our next issue will be on January 2, 2020.

PLRC SIG

PLRC Tumorigenesis SIG

Tue, 1/7/2020

12:00 to 1:00 pm

S123 BST

Dr. Michael Nalesnik - Molecular Classification of HCC

Dr. Silvia Liu - Novel Biomarker Discovery in HCC

Pizza will be provided.

The full schedule of Enrichment activities is posted on **https://www.livercenter.pitt.edu/events**.

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:

Fu CP, Ali H, **Rachakonda VP**, Oczypok EA, DeLany JP, Kershaw EE. The ZJU index is a powerful surrogate marker for NAFLD in severely obese North American women. PLoS One. 2019 Nov 26;14(11):e0224942. doi: 10.1371/journal.pone.0224942. eCollection 2019. PubMed PMID: 31770380.

ABSTRACT

INTRODUCTION: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the western world and is highly associated with multiple cardiometabolic complications. The Zhejiang University (ZJU) index was first developed to predict NAFLD in Chinese populations, where it was shown to have better predictive value than other currently used indices. The aims of the present study were to 1) determine the diagnostic accuracy of ZJU index in identifying NAFLD in a well-phenotyped cohort of obese middle-aged American women and 2) compare its performance with other non-invasive indices for NAFLD identification.

METHODS: To achieve this goal, we performed a retrospective analysis of a prospectively-collected cohort of participants enrolled in a weight loss trial for severe obesity (RENEW, clinicaltrials.gov identifier: NCT00712127). One hundred and seven women between the age of 30 and 55 with obesity class II (BMI 35-39.9 kg/m2) or class III (BMI ≥ 40 kg/m2) were recruited for analyses. Hepatic steatosis was measured using liver/spleen attenuation ratio (L/S ratio) from unenhanced abdominal computed tomography. Beside ZJU index, hepatic steatosis index (HSI), lipid accumulation production index (LAPI), and visceral adiposity index (VAI) were also determined and to compare their performance in predicting NAFLD.

RESULTS: Of 107 obese women in the study, 40 (37.4%) met imaging criteria for NAFLD using cut-off value of L/S ratio < 1.1. The ZJU index was positively correlated with HIS, LAPI, but not VAI. The area under the curve was highest for the ZJU index (AUC = 0.742, 95% CI:0.647-0.837), followed by HSI (AUC = 0.728, 95% CI:0.631-0.825), LAPI (AUC = 0.682, CI:0.583-0.781), and VAI (AUC = 0.621, 95% CI:0.518-0.725), respectively, using the Youden method.

CONCLUSION: The ZJU index is a powerful surrogate marker for NAFLD in severely obese western females and its predictive value was better than that of other commonly used indices for predicting NAFLD. Our study is the first to suggest that the ZJU index could be a promising model for use in western as well as Chinese populations.

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

Original Article:

Singhi AD, Wood LD, Parks E, Torbenson MS, Felsenstein M, Hruban

RH, Nikiforova MN, Wald AI, Kaya C, Nikiforov YE, Favazza L, He J, McGrath K, Fasanella KE, Brand RE, Lennon AM, **Furlan A**, Dasyam AK, Zureikat AH, Zeh HJ, Lee K, Bartlett DL, Slivka A. Recurrent Rearrangements in PRKACA and PRKACB in Intraductal Oncocytic Papillary Neoplasms of the Pancreas and Bile Duct. Gastroenterology. 2019 Oct 30. pii: S0016-5085(19)41481-9. doi: 10.1053/j.gastro.2019.10.028. PubMed PMID: 31678302.

ABSTRACT

BACKGROUND and AIMS: Intraductal oncocytic papillary neoplasms (IOPNs) of the pancreas and bile duct contain epithelial cells with numerous, large mitochondria and are cystic precursors to pancreatic ductal adenocarcinoma (PDAC) and cholangiocarcinoma (CCA), respectively. However, IOPNs do not have the genomic alterations found in other pancreatobiliary neoplasms. In fact, no recurrent genomic alterations have been described in IOPNs. PDACs without activating mutations in KRAS contain gene rearrangements, so we investigated whether IOPNs have recurrent fusions in genes.

METHODS: We analyzed 20 resected pancreatic IOPNs and 3 resected biliary IOPNs using a broad RNA-based targeted sequencing panel to detect cancer-related fusion genes. Four invasive PDACs and 2 intrahepatic cholangiocarcinomas from the same patients as the IOPNs, were also available for analysis. Samples of pancreatic cyst fluid (n=5, collected before surgery) and bile duct brushings (n=2) were analyzed for translocations. For comparison, we analyzed pancreatobiliary lesions from 126 patients without IOPN (controls).

RESULTS: All IOPNs evaluated were found to have recurring fusions of ATP1B1-PRKACB (n = 13), DNAJB1-PRKACA (n = 6), or ATP1B1-PRKACA (n = 4). These fusions were also found in corresponding invasive PDACs and intrahepatic cholangiocarcinomas, as well as in matched pancreatic cyst fluid and bile duct brushings. These gene

rearrangements were absent from all 126 control pancreatobiliary lesions.

CONCLUSIONS: We identified fusions in PRKACA and PRKACB genes in pancreatic and biliary IOPNs, as well as in PDACs and pancreatic cyst fluid and bile duct cells from the same patients. We did not identify these gene fusions in 126 control pancreatobiliary lesions. These fusions might be used to identify patients at risk for IOPNs and their associated invasive carcinomas.

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

Original Article:

Edmunds LR, Huckestein BR, Kahn M, Zhang D, Chu Y, Zhang Y, Wendell SG, Shulman GI, **Jurczak MJ**. Hepatic insulin sensitivity is improved in high-fat diet-fed Park2 knockout mice in association with increased hepatic AMPK activation and reduced steatosis. Physiol Rep. 2019 Nov;7(21):e14281. doi: 10.14814/phy2.14281. PubMed PMID: 31724300.

ABSTRACT

Park2 is an E3 ubiquitin ligase known for its role in mitochondrial quality control via the mitophagy pathway. Park2 KO mice are protected from diet-induced obesity and hepatic insulin sensitivity is improved in high-fat diet (HFD)-fed Park2 KO mice even under body weight-matched conditions. In order to better understand the cellular mechanism by which Park2 KO mice are protected from diet-induced hepatic insulin resistance, we determined changes in multiple pathways commonly associated with the pathogenesis of insulin resistance, namely levels of bioactive lipid species, activation of the endoplasmic reticulum (ER) stress response and changes in cytokine levels and signaling. We report for the first time that whole-body insulin sensitivity is unchanged in regular

chow (RC)-fed Park2 KO mice, and that liver diacylglycerol levels are reduced and very-long-chain ceramides are increased in Park2 KO mice fed HFD for 1 week. Hepatic transcriptional markers of the ER stress response were reduced and plasma tumor necrosis factor-α (TNFα), interleukin-6 and -10 (IL6, IL10) were significantly increased in HFD-fed Park2 KO mice; however, there were no detectable differences in hepatic inflammatory signaling pathways between groups. Interestingly, hepatic adenylate charge was reduced in HFD-fed Park2 KO liver and was associated increased activation of AMPK. These data suggest that negative energy balance that contributed to protection from obesity during chronic HFD manifested at the level of the hepatocyte during short-term HFD feeding and contributed to the improved hepatic insulin sensitivity.

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

Award:

Dr. Tirthadipa Pradhan-Sundd has received the 2020 AGA-Elsevier Pilot Research Award for her project, "Molecular mechanism of sickle cell anemia induced chronic liver injury." Congratulations!

Original Article:

Xie Y, Barbosa ACS, Xu M, Oberly PJ, Ren S, Gibbs RB, Poloyac SM, Song W, Fan J, **Xie W**. Hepatic Estrogen Sulfotransferase Distantly Sensitizes Mice to Hemorrhagic Shock-Induced Acute Lung Injury. Endocrinology. 2019 Dec 14. pii: bqz031. doi: 10.1210/endocr/bqz031. [Epub ahead of print] PMID: 31837219

ABSTRACT

Hemorrhagic shock (HS) is a potential life-threatening condition that may lead to injury to multiple organs, including the lung. The estrogen sulfotransferase (EST, or SULT1E1) is a conjugating enzyme

that sulfonates and deactivates estrogens. In this report, we showed that the expression of Est was markedly induced in the liver, but not in the lung of female mice subject to hemorrhagic shock and resuscitation (HS/R). Genetic ablation or pharmacological inhibition of Est effectively protected female mice from HS-induced acute lung injury (ALI), including interstitial edema, neutrophil mobilization and infiltration, and inflammation. The pulmonoprotective effect Est ablation or inhibition was sex-specific, because the HS-induced ALI was not affected in male Est-/- mice. Mechanistically, the pulmonoprotective phenotype in female Est-/- mice was accompanied by increased lung and circulating levels of estrogens, attenuated pulmonary inflammation, and inhibition of neutrophil mobilization from the bone marrow and infiltration to the lung, whereas the pulmonoprotective effect was abolished upon ovariectomy, suggesting that the pulmonoprotective effect was estrogen dependent. The pulmonoprotective effect of Est ablation was also tissue-specific, as loss of Est had little effect on HS-induced liver injury. Moreover, transgenic reconstitution of human EST in the liver of global Est-/- mice abolished the pulmonoprotective effect, suggesting that it is the EST in the liver that sensitizes mice to HS-induced ALI. Taken together, our results revealed a sex- and tissue-specific role of EST in HS-induced ALI. Pharmacological inhibition of EST may represent an effective approach to manage HS-induced ALI.

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

Funding Opportunities

Limited Competition: NIDDK Program Projects (P01 Clinical Trial Optional)

(PAR-20-075)

National Institute of Diabetes and Digestive and Kidney Diseases

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Judith Graham Pool (JGP) Postdoctoral Research Fellowship

National Hemophilia Foundation (NHF)

Our mailing address is:

Pittsburgh Liver Research Center

200 Lothrop St. | Pittsburgh, PA 15261