Liver Digest

A weekly update of PLRC happenings

August 8, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Michael Oertel

In this issue

Today's Seminar

PLRC Seminar Series

Thursday, August 8, 2019

Noon - 1:00 p.m.

S120 BST

Kenichi Ikejima, MD, PhD

Professor of Medicine, Department of Gastroenterology

Juntendo University Graduate School of Medicine, Japan

"Pathophysiological basis of steatohepatitis and therapeutic approaches"

Pizza will be provided.

PLRC Meet & Greet - September 12

Please save the date for the **PLRC's Meet and Greet!**

September 12, 2019

4:30-7:30 p.m.

Ballroom A - University Club

123 University Place

Pittsburgh, PA 15260

Invitations containing program details and requesting RSVPs will be forthcoming.

Dr. Alex Soto-Gutierrez's work receives international attention

Dr. Alex Soto-Gutierrez's team published a manuscript in Cell Metabolism on "Generation of Human Fatty Livers Using Custom-Engineered Induced Pluripotent Stem Cells with Modifiable SIRT1 Metabolism." The citation, abstract, and link to full text are below.

Special thanks to Dr. Erin Hare of the UPMC Media Relations department for compiling this list of media stories on the article. In addition, Erin let us know that our local CBS station, KDKA, was in the lab yesterday filming a story that will run sometime in the next month or so.

National Geographic
Spektrum der Wissenschaft
El Confidencial
XinhuaNet
La Repubblica
Wirtualna Polska
The Conversation
Houston Chronicle
Raw Story
Down to Earth
Devdiscourse
Infosalus
Technology Networks
Medical Xpress

Alexandra Collin de l'Hortet, Kazuki Takeishi, Jorge Guzman-Lepe, Kazutoyo Morita, Abhinav Achreja, Branimir Popovic, Yang Wang, Kan Handa, Anjali Mittal, Noah Meurs, Ziwen Zhu, Frank Weinberg, Michael Salomon, **Ira J.Fox**, Chu-Xia Deng, Deepak Nagrath, **Alejandro Soto-Gutierrez**. Generation of Human Fatty Livers Using Custom-Engineered Induced Pluripotent Stem Cells with Modifiable SIRT1 Metabolism. Cell Metabolism Volume 30, Issue 2, 6 August 2019, Pages 385-401.e9.

ABSTRACT
The mechanisms by which steatosis of the liver progresses to non-alcoholic

steatohepatitis and end-stage liver disease remain elusive. Metabolic derangements in hepatocytes controlled by SIRT1 play a role in the development of fatty liver in inbred animals. The ability to perform similar studies using human tissue has been limited by the genetic variability in man. We generated human induced pluripotent stem cells (iPSCs) with controllable expression of SIRT1. By differentiating edited iPSCs into hepatocytes and knocking down SIRT1, we found increased fatty acid biosynthesis that exacerbates fat accumulation. To model human fatty livers, we repopulated decellularized rat livers with human mesenchymal cells, fibroblasts, macrophages, and human SIRT1 knockdown iPSC-derived hepatocytes and found that the human iPSC-derived liver tissue developed macrosteatosis, acquired proinflammatory phenotype, and shared a similar lipid and metabolic profiling to human fatty livers. Biofabrication of genetically edited human liver tissue may become an important tool for investigating human liver biology and disease.

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

Faculty Collaboration Highlights

Original Article:

Ruiz de Galarreta M, Bresnahan E, Molina-Sanchez P, Lindblad KE, Maier B, Sia D, Puigvehi M, Miguela V, Casanova-Acebes M, Dhainaut M, Villacorta-Martin C, **Singhi AD**, Moghe A, von Felden J, Tal Grinspan L, Wang S, Kamphorst AO, **Monga SP**, Brown BD, Villanueva A, Llovet JM, Merad M, Lujambio A. β-catenin activation promotes immune escape and resistance to anti-PD-1 therapy in hepatocellular carcinoma. Cancer Discov. 2019 Jun 11. pii: CD-19-0074. doi: 10.1158/2159-8290.CD-19-0074. [Epub ahead of print] PubMed PMID: 31186238.

ABSTRACT

PD-1 immune checkpoint inhibitors have produced encouraging results in patients with hepatocellular carcinoma (HCC). However, what determines resistance to anti-PD-1 therapies is unclear. We created a novel genetically engineered mouse model of HCC that enables interrogation of how different genetic alterations affect immune surveillance and response to immuno-therapies. Expression of exogenous antigens in MYC;Trp53 -/- HCCs led to T cell-mediated immune surveillance, which was accompanied by decreased tumor formation and increased survival. Some antigen-expressing MYC;Trp53 -/- HCCs escaped the immune system by upregulating the β-catenin (CTNNB1) pathway.

Accordingly, expression of exogenous antigens in MYC;CTNNB1 HCCs had no effect, demonstrating that β-catenin promoted immune escape, which involved defective recruitment of dendritic cells and consequently impaired T-cell activity. Expression of chemokine CCL5 in antigen-expressing MYC;CTNNB1 HCCs restored immune surveillance. Finally, β-catenin-driven tumors were resistant to anti-PD-1. In summary, β-catenin activation promotes immune escape and resistance to anti-PD-1 and could represent a novel biomarker for HCC patient exclusion.
SIGNIFICANCE: Determinants of response to anti-PD-1 immunotherapies in HCC are poorly understood. Using a novel mouse model of HCC, we show that β-catenin activation promotes immune evasion and resistance to anti-PD-1 therapy and could potentially represent a novel biomarker for HCC patient exclusion. See related commentary by Berraondo et al., p. 1003.

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

Original Article:
Yang C, Sun P, Deng M, Loughran P, Li W, Yi Z, Li S, Zhang X, Fan J, **Billiar TR, Scott MJ**. Gasdermin D protects against noninfectious liver injury by regulating apoptosis and necroptosis. Cell Death Dis. 2019 Jun 17;10(7):481. doi: 10.1038/s41419-019-1719-6. PubMed PMID: 31209224; PubMed Central PMCID: PMC6579760.

ABSTRACT
Gasdermin D (GsdmD) was recently identified as the executioner of pyroptotic inflammatory cell death, and is a substrate for caspases-1 and 11. GsdmD is detrimental in lethal endotoxemia but protective in bacterial sepsis. However, little is known about its role during noninfectious/sterile injuries. In this study, we examined the contribution of GsdmD using WT and GsdmD-/- mice in two models of noninfectious liver injury: hemorrhagic shock with resuscitation (HS/R) and acetaminophen (APAP) overdose. GsdmD-/- mice had significantly increased liver damage at 6 h after HS/R or APAP vs WT, shown by significantly elevated ALT level and extended areas of cell death in liver. Caspase-8, a mediator of multiple cell death pathways, was highly elevated in GsdmD-/- mice after injury. Significantly increased cleavage of caspase-8 and subsequent high levels of apoptosis were found in livers of GsdmD-/- mice after HS/R, a relatively mild ROS-induced liver injury. However, during more severe APAP-mediated ROS-induced liver injury, caspase-8 cleavage in GsdmD-/- liver was

inhibited compared with WT, resulting in accumulation of pro-caspase-8 and increased levels of necroptosis. Our findings indicate a novel hepatoprotective role for GsdmD in noninfectious inflammation models via regulation of caspase-8 expression and downstream cell death pathways. The effects of GsdmD protection are likely injury specific and may also depend on injury severity and levels of ROS produced. These data suggest modulation of GsdmD/caspase-8 may be a novel therapeutic option in ROS-mediated liver injury.

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

Inside View Article:

Dirk J van der Windt, Gregory C Wilson, Ioannis A Ziogas, Samer Tohme, **Alessandro Furlan, Michael A Nalesnik, David A Geller**. Mass in a fatty liver Frontline Gastroenterology Published Online First: 02 August 2019. doi: 10.1136/flgastro-2019-101284.

INTRODUCTION

A 39-year-old man was referred to our clinic for liver diseases for a liver mass incidentally found on CT done to rule out kidney stones (figure 1A). In our clinic, he was asymptomatic with regular bowel habits. He denied episodes of jaundice, did not have skin tattoos, never smoked or used illicit drugs and rarely consumed alcohol. His lifestyle was sedentary, and his diet consisted predominantly of fast food. His medical history included arterial hypertension and hyperlipidaemia. Several years prior, he had undergone a laparoscopic cholecystectomy. His obese abdomen (body mass index 36 kg/m2) was non-tender to palpation. On laboratory analysis, white blood cell count, haemoglobin, platelet count, bilirubin, liver transaminases and international normalised ratio (INR) were within normal limits. Hepatitis A, B and C serologies were negative. Serum tumour markers alpha-fetoprotein and CA19-9 were not elevated. Haemoglobin A1c was 6.1%. To further characterise his liver mass, contrast-enhanced MRI was performed, which revealed a fatty liver with a 2.5 cm lesion in segment 4B (figure 1B–D). During laparoscopic surgical resection, a cystic-appearing mass was encountered that drained thick mucus on decompression (figure 2).

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

Original Article:

Yu YP, Tsung A, **Liu S, Nalesnick M, Geller D, Michalopoulos G, Luo JH**. Detection of fusion transcripts in the serum samples of patients with hepatocellular carcinoma. Oncotarget. 2019 May 21;10(36):3352-3360. eCollection 2019 May 21. PubMed PMID: 31164957; PubMed Central PMCID: PMC6534357.

ABSTRACT
Hepatocellular carcinoma is one of the most lethal cancers in the United States. Early detection of the disease is crucial for reducing the mortality of this malignancy. Recently, we identified a panel of fusion genes present in several types of human cancers, including hepatocellular carcinoma. Among 8 fusion genes, MAN2A1-FER, TRMT11-GRIK2 and CCNH-C5orf30 appear most frequently in hepatocellular carcinoma samples. In this study, we showed that the fusion transcripts of MAN2A1-FER, CCNH-C5orf30 and SLC45A2-AMACR were detected in the serum samples of liver cancer patients as circulating cell-free RNA. The distributions of these gene fusion RNA fragments largely matched those of the primary HCC samples. In contrast, the sera of all healthy individuals free of human malignancies were shown to be negative for these fusion genes. These results suggest that gene fusion RNA is frequently shed from liver cancer cells. The detection of serum cell-free fusion transcripts may provide a new approach to aid in the diagnosis, follow-up or therapy of liver cancers.

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

Funding Opportunities

Research Awards: Bridge Award

American Association for the Study of Liver Diseases (AASLD)

NIDDK Central Repositories Non-renewable Sample Access (X01 Clinical Trial Not Allowed)

(PAR-19-319)

National Institute of Diabetes and Digestive and Kidney Diseases

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