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# Liver Digest

A weekly update of PLRC happenings

February 28, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. David Whitcomb

# In this issue



## Next Week's Seminars

**PLRC Seminar Series - Dr. Natalie Torok**

Tues, March 5, noon-1:00 pm

Berkman Boardroom, N727 Montefiore

**Natalie J. Torok, MD, MSc**

Professor of Medicine, Gastroenterology and Hepatology

Director of the T32 Program, Division of Gastroenterology and Hepatology

Stanford University School of Medicine

**Aging and NASH**

*This activity has been approved for AMA PRA Category 1 Credit. #6242 Liver Center Seminars.*

*Pizza will be provided.*

This session will not be available via webcast.

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

## Liver Cancer Conference - March 9

Community Liver Allicance Liver Cancer Conference
Saturday, March 9, 2019 | 7:30 a.m. - 3:00 p.m.
Wyndham Grand Hotel, Pittsburgh, PA
*CME Accredited*

For schedule, speakers, and details, please visit the PLRC website:
**http://www.livercenter.pitt.edu/livercancer-conference**

To register, please visit the CLA website:
**http://www.communityliveralliance.org/liver-cancerconference**

## 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:

**Yuan JM**, Grouls M, Carmella SG, Wang R, Heskin A, Jiang Y, Tan YT, Adams-Haduch J, Gao YT, Hecht SS. Prediagnostic levels of urinary 8-epi-prostaglandin F2α and prostaglandin E2 metabolite, biomarkers of oxidative damage and inflammation, and risk of hepatocellular carcinoma. Carcinogenesis. 2019 Jan 5. doi: 10.1093/carcin/bgy180. [Epub ahead of print] PubMed PMID: 30615102.

ABSTRACT

Chronic inflammation and oxidative stress play pivotal roles in the pathogenesis of hepatocellular carcinoma (HCC). We conducted a nested case-control study of 347 HCC cases and 691 matched controls within a prospective cohort of 18 244 Chinese men in Shanghai, China. The concentrations of 8-epi-prostaglandin F2α (8-epi-PGF2α), a biomarker of oxidative stress, and prostaglandin E2 (PGE2) metabolite (PGE-M), a biomarker of the inflammation mediator PGE2, were determined in baseline urine samples using validated mass spectrometry assays. 8-epi-PGF2α levels were significantly higher in HCC cases than control subjects (geometric means 0.92 versus 0.80 pmol/mg creatinine, $P < 0.001$). The relative risks of developing HCC for the highest relative to the lowest quartile of 8-epi-PGF2α were 2.55 (95% confidence interval = 1.62-4.01, Ptrend < 0.001). This positive 8-epi-PGF2α-HCC risk association was independent of smoking status, alcohol consumption and hepatitis B or liver cirrhosis and was present 10 years before the clinical manifestation of HCC. This study did not find any significant association between urinary PEG-M and HCC risk. This study provides direct evidence in support of the critical role of oxidative stress in the development of HCC regardless of its underlying causes.

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

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Original Article:

Chen L, Liu Q, Tang Q, Kuang J, Li H, Pu S, Wu T, Yang X, Li R, Zhang J, Zhang Z, Huang Y, Li Y, Zou M, Jiang W, Li T, Gong M, Zhang L, Wang H, Qu A, **Xie W**, He J. Hepatocyte-specific Sirt6 deficiency impairs ketogenesis. J Biol Chem. 2019 Feb 1;294(5):1579-1589. doi: 10.1074/jbc.RA118.005309. Epub 2018 Dec 10. PubMed PMID: 30530497; PubMed Central PMCID: PMC6364758.

ABSTRACT

Sirt6 is an NADH (NAD+)-dependent deacetylase with a critical role in hepatic lipid metabolism. Ketogenesis is controlled by a signaling network of hepatic lipid metabolism. However, how Sirt6 functions in ketogenesis remains unclear. Here, we demonstrated that Sirt6 functions as a mediator of ketogenesis in response to a fasting and ketogenic diet (KD). The KD-fed hepatocyte-specific Sirt6 deficiency (HKO) mice exhibited impaired ketogenesis, which was due to enhanced Fsp27 (fat-specific induction of protein 27), a protein known to regulate lipid metabolism. In contrast, overexpression of Sirt6 in mouse primary hepatocytes promoted ketogenesis. Mechanistically, Sirt6 repressed Fsp27β expression by interacting with Crebh (cAMP response element–binding protein H) and preventing its recruitment to the Fsp27β gene promoter. The KD-fed HKO mice also showed exacerbated hepatic steatosis and inflammation. Finally, Fsp27 silencing rescued hypoketonemia and other metabolic phenotypes in KD-fed HKO mice. Our data suggest that the Sirt6–Crebh–Fsp27 axis is pivotal for hepatic lipid metabolism and inflammation. Sirt6 may be a pharmacological target to remedy metabolic diseases.

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

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Original Article:

Zhang J, Liu P, Tao J, Wang P, Zhang Y, Song X, Che L, Sumazin P, Ribback S, Kiss A, Schaff Z, Cigliano A, Dombrowski F, Cossu C,

Pascale RM, Calvisi DF, **Monga SP**, Chen X. TEA domain transcription factor 4 (TEAD4) is the major mediator of Yap oncogenic activity in mouse and human hepatoblastoma. Am J Pathol. 2019 Feb 19. pii: S0002-9440(18)30776-4. doi: 10.1016/j.ajpath.2019.01.016. [Epub ahead of print] PMID: 30794805

ABSTRACT
Hepatoblastoma (HB) is the most common type of pediatric liver cancer. Activation of Yes-associated protein (YAP) has been implicated in HB molecular pathogenesis. The transcriptional co-activator Yap regulates downstream gene expression through interaction with the TEA domain (TEAD) proteins. Nonetheless, YAP also displays functions that are independent of its transcriptional activity. The underlying molecular mechanisms by which Yap promotes HB development remain elusive. In the current study, we demonstrated that blocking TEAD function via the dominant negative form of TEAD2 (dnTEAD2) abolishes Yap-driven HB formation in mice and restrains human HB growth in vitro. When TEAD2 DNA binding domain was fused with VP16 transcriptional activation domain (TEAD2VP16), it synergized with activated β-catenin (ΔN90-β-catenin) to promote HB formation in vivo. Among TEAD genes, silencing of TEAD4 consistently inhibited tumor growth and Yap target gene expression in HB cell lines. Furthermore, TEAD4 mRNA expression was significantly higher in human HB lesions when compared with corresponding non-tumorous liver tissues. Human HB specimens also exhibited strong nuclear immunoreactivity for TEAD4. Altogether, data demonstrate that TEAD-mediated transcriptional activity is both sufficient and necessary for Yap-driven HB development. TEAD4 is the major TEAD isoform and Yap partner in human HB. Targeting TEAD4 may represent an effective treatment option for human HB.

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

Original Article:

Min Q, Molina L, Li J, Adebayo Michael AO, Russell JO, Preziosi ME, Singh S, Poddar M, Matz-Soja M, **Ranganathan S**, **Bell AW**, Gebhardt R, Gaunitz F, Yu J, Tao J, **Monga SP**. β-Catenin and yes-associated protein 1 cooperate in hepatoblastoma pathogenesis. Am J Pathol. 2019 Feb 19. pii: S0002-9440(18)30759-4. doi: 10.1016/j.ajpath.2019.02.002. [Epub ahead of print] PMID: 30794807

ABSTRACT

Hepatoblastoma (HB), the most common pediatric primary liver neoplasm, show nuclear localization of β-catenin and yes-associated protein1 (YAP1) in almost 80% of the cases. Co-expression of constitutively active S127A-YAP1 and ΔN90 deletion-mutant-β-catenin (YAP1-ΔN90-β-catenin) causes HB in mice. Since heterogeneity in downstream signaling is being identified owing to mutational differences even in β-catenin gene alone, we investigated if co-expression of point-mutants of β-catenin (S33Y or S45Y) with S127A-YAP1 led to similar tumors as YAP1-ΔN90-β-catenin. Co-expression of S33Y/S45Y-β-catenin and S127A-YAP1 led to activation of Yap and Wnt signaling and development of HB with 100% mortality by 13 to 14 weeks. Co-expression with YAP1-S45Y/S33Y-β-catenin of the dominant-negative (dn) TCF4 or dnTEAD2, the respective surrogate transcription factors, prevented HB development. Although histologically similar, HB in YAP1-S45Y/S33Y-β-catenin, unlike YAP1-ΔN90-β-catenin HB were glutamine synthetase (GS)-positive. However, both ΔN90-β-catenin and point-mutant-β-catenin comparably induced GS-luciferase reporter in vitro. Finally, using a previously reported 16-gene signature, it was shown that YAP1-ΔN90-β-catenin HB tumors exhibit genetic similarities with more proliferative, less differentiated, GS-negative HB patient tumors, whereas YAP1-S33Y/S45Y-β-catenin HB exhibit heterogeneity and clustered with both well-differentiated GS-positive and

proliferative GS-negative patient tumors. Thus, we demonstrate that β-catenin point mutants can also collaborate with YAP1 in HB development, albeit with distinct molecular profile from the deletion mutant, which may have implications in both biology and therapy.

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

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Original Article:

**Zamora R**, Korff S, Mi Q, Barclay D, Schimunek L, Zucca R, Arsiwalla XD, Simmons RL, Verschure P, **Billiar TR**, **Vodovotz Y**. A computational analysis of dynamic, multi-organ inflammatory crosstalk induced by endotoxin in mice. PLoS Comput Biol. 2018 Nov 6;14(11):e1006582. doi: 10.1371/journal.pcbi.1006582. eCollection 2018 Nov. PubMed PMID: 30399158; PubMed Central PMCID: PMC6239343.

ABSTRACT:
Bacterial lipopolysaccharide (LPS) induces an acute inflammatory response across multiple organs, primarily via Toll-like receptor 4 (TLR4). We sought to define novel aspects of the complex spatiotemporal dynamics of LPS-induced inflammation using computational modeling, with a special focus on the timing of pathological systemic spillover. An analysis of principal drivers of LPS-induced inflammation in the heart, gut, lung, liver, spleen, and kidney to assess organ-specific dynamics, as well as in the plasma (as an assessment of systemic spillover), was carried out using data on 20 protein-level inflammatory mediators measured over 0-48h in both C57BL/6 and TLR4-null mice. Using a suite of computational techniques, including a time-interval variant of Principal Component Analysis, we confirm key roles for cytokines such as tumor necrosis factor-α and interleukin-17A, define a temporal hierarchy of organ-localized inflammation, and infer the point at which organ-localized inflammation spills over

systemically. Thus, by employing a systems biology approach, we obtain a novel perspective on the time- and organ-specific components in the propagation of acute systemic inflammation.

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

## Funding Opportunities

**Coulter - PLRC Joint Award**

The University of Pittsburgh & UPMC Pittsburgh Liver Research Center (PLRC) is pleased to announce a new translational grant program in collaboration with the Coulter TPII Program (Coulter) at the University of Pittsburgh. In September of 2019, the PLRC/Coulter will award up to one $50,000 grant, aimed at developing the commercial potential of healthcare solutions that are based on innovative technologies related to liver health, including disease diagnosis, surgery, treatment, and public health. One-Page LOI Submission: Deadline - 5:00 p.m. Friday, March 15, 2019.

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Advancing Cancer Immunotherapy by Mitigating Immune-related Adverse Events (irAEs) (U01 Clinical Trial Not Allowed)

**(RFA-CA-19-044)**

National Cancer Institute
National Institute of Allergy and Infectious Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Diseases

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