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Liver Digest

A weekly update of PLRC happenings

November 14, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Peter Lucas

In this issue

Next Week's Seminars

Transplantation Grand Rounds

Friday, November 15, 2019

8:00am

LHAS Auditorium, located in Montefiore University Hospital, Seventh Floor.

Peter P. Reese, MD, MSCE
Associate Professor of Medicine & Epidemiology
Perelman School of Medicine
University of Pennsylvania

Transplanting Hepatitis-C Infected Organs into Uninfected Recipients – Past, Present and Future

Continental breakfast will be provided.

PLRC Seminar Series

Tue, 11/19/2019

12:00 to 1:00 p.m.
S120 BST

Tatiana Kisseleva, MD, PhD

Associate Adjunct Professor of Surgery
School of Health Sciences, University of California, San Diego

IL-17 Signaling in Steatotic Hepatocytes and Macrophages Promotes Alcoholic Liver Disease and Hepatocellular Carcinoma

Pizza will be provided.
This activity has been approved for AMA PRA Category 1 credit.
#6242-Liver Center Seminars.

New Process for CME Credit for Seminars

The record-keeping for UPMC's CME accreditation is being migrated to a new on-line system. Beginning with Dr. Tatiana Kisseleva's seminar on November 19, all PLRC seminars will use the new tracking system. In the new system, you will be able to record your attendance at the seminar using your phone. I will provide a unique SMS code at each seminar for this purpose.

If you would like to receive CME credit for the PLRC seminars, please follow this link for instructions on setting up your account and using the new system: **https://cce.upmc.com/ . Please note that the old system is being discontinued as of November 30.**

Post-Doc Position Available

Dr. Daniela Sia of the Icahn School of Medicine at Mount Sinai is seeking a post-doc to begin January 2020. The official job announcement is **available here**.

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Editorial:**Duncan AW**. Single Cell and Bulk Transcriptome Profiling Reveals Unique Features of Diploid and Polyploid Hepatocytes. Cell Mol Gastroenterol Hepatol. 2019 Oct 22. pii: S2352-345X(19)30126-2. doi: 10.1016/j.jcmgh.2019.09.008. PubMed PMID: 31654613.

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

Original Article:

Klompenhouwer AJ, Dwarkasing RS, Doukas M, Pellegrino S, Vilgrain V, Paradis V, Soubrane O, Beane JD, **Geller DA, Nalesnik MA**, Tripke V, Lang H, Schmelzle M, Pratschke J, Schöning W, Beal E, Sun S, Pawlik TM, de Man RA, Ijzermans JNM. Hepatic angiomyolipoma: an international multicenter analysis on diagnosis, management and outcome. HPB (Oxford). 2019 Oct 13. pii: S1365-182X(19)30716-6. doi: 10.1016/j.hpb.2019.09.004. PubMed PMID: 31619346.

ABSTRACT

BACKGROUND: Hepatic angiomyolipoma (HAML) may easily be misdiagnosed as a malignancy. The study aim was to assess diagnostic dilemmas, clinical management and outcome of this rare

tumor.

METHODS: This retrospective international multicenter study included all patients with pathologically proven HAML diagnosed between 1997 and 2017. Data on patient characteristics, diagnostic work-up, management and follow-up were analyzed.

RESULTS: Thirty-eight patients were included, 32 female. Median age was 56yrs (i.q.r. 43-64) and median HAML-diameter was 57.5 mm (i.q.r. 38.5-95.3). Thirty patients had undergone CT and 27/38 MRI of the liver, diagnostic biopsy was performed in 19/38. Initial diagnosis was incorrect in 15/38 patients, of which 13 were thought to have malignancy. In 84% biopsy resulted in a correct preoperative diagnosis. Twenty-nine patients were managed with surgical resection, 4/38 with surveillance and 3/38 with liver transplantation. Recurrence after resection occurred in two cases. No HAML related deaths or progression to malignancy were documented.

CONCLUSION: HAML diagnosis proved problematic even in hepatobiliary expertise centers. Biopsy is indicated and may provide valuable additional information when HAML diagnosis is considered on cross-sectional imaging, especially when surgical resection imposes a risk of complications. Conservative management with regular imaging follow-up might be justified when biopsy confirms (classic type) HAML.

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

Original Article:
Chiba T, Peasley KD, Cargill KR, Maringer KV, Bharathi SS, Mukherjee E, Zhang Y, Holtz A, Basisty N, Yagobian SD, Schilling B, **Goetzman ES**, Sims-Lucas S. Sirtuin 5 Regulates Proximal Tubule

Fatty Acid Oxidation to Protect against AKI. J Am Soc Nephrol. 2019 Oct 1. pii: ASN.2019020163. doi: 10.1681/ASN.2019020163. PubMed PMID: 31575700.

ABSTRACT

BACKGROUND: The primary site of damage during AKI, proximal tubular epithelial cells, are highly metabolically active, relying on fatty acids to meet their energy demands. These cells are rich in mitochondria and peroxisomes, the two organelles that mediate fatty acid oxidation. Emerging evidence shows that both fatty acid pathways are regulated by reversible posttranslational modifications, particularly by lysine acylation. Sirtuin 5 (Sirt5), which localizes to both mitochondria and peroxisomes, reverses post-translational lysine acylation on several enzymes involved in fatty acid oxidation. However, the role of the Sirt5 in regulating kidney energy metabolism has yet to be determined.

METHODS: We subjected male Sirt5-deficient mice (either +/- or -/-) and wild-type controls, as well as isolated proximal tubule cells, to two different AKI models (ischemia-induced or cisplatin-induced AKI). We assessed kidney function and injury with standard techniques and measured fatty acid oxidation by the catabolism of 14C-labeled palmitate to 14CO2.

RESULTS: Sirt5 was highly expressed in proximal tubular epithelial cells. At baseline, Sirt5 knockout (Sirt5-/-) mice had modestly decreased mitochondrial function but significantly increased fatty acid oxidation, which was localized to the peroxisome. Although no overt kidney phenotype was observed in Sirt5-/- mice, Sirt5-/- mice had significantly improved kidney function and less tissue damage compared with controls after either ischemia-induced or cisplatin-induced AKI. This coincided with higher peroxisomal fatty acid oxidation compared with mitochondria fatty acid oxidation in the

Sirt5-/- proximal tubular epithelial cells.

CONCLUSIONS: Our findings indicate that Sirt5 regulates the balance of mitochondrial versus peroxisomal fatty acid oxidation in proximal tubular epithelial cells to protect against injury in AKI. This novel mechanism might be leveraged for developing AKI therapies.

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

Original Article:

Lear TB, McKelvey AC, Evankovich JW, Rajbhandari S, Coon TA, Dunn SR, Londino JD, McVerry BJ, Zhang Y, Valenzi E, Burton CL, Gordon R, Gingras S, Lockwood KC, **Jurczak MJ**, Lafyatis R, Shlomchik MJ, Liu Y, Chen BB. KIAA0317 regulates pulmonary inflammation through SOCS2 degradation. JCI Insight. 2019 Oct 3;4(19). pii: 129110. doi: 10.1172/jci.insight.129110. PubMed PMID: 31578312.

ABSTRACT

Dysregulated proinflammatory cytokine release has been implicated in the pathogenesis of several life-threatening acute lung illnesses such as pneumonia, sepsis, and acute respiratory distress syndrome. Suppressors of cytokine signaling proteins, particularly SOCS2, have recently been described as antiinflammatory mediators. However, the regulation of SOCS2 protein has not been described. Here we describe a mechanism of SOCS2 regulation by the action of the ubiquitin E3 ligase KIAA0317. KIAA0317-mediated degradation of SOCS2 exacerbated inflammation in vitro, and depletion of KIAA0317 in vivo ameliorated pulmonary inflammation. KIAA0317-knockout mice exhibited resistance to LPS-induced pulmonary inflammation, while KIAA03017 reexpression mitigated this effect. We uncovered a small molecule inhibitor of KIAA0317 protein (BC-1365) that prevented SOCS2 degradation and attenuated LPS- and P. aeruginosa-induced

lung inflammation in vivo. These studies show KIAA0317 to be a critical mediator of pulmonary inflammation through its degradation of SOCS2 and a potential candidate target for therapeutic inhibition.

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

Funding Opportunity

NCI Small Grants Program for Cancer Research for Years 2020, 2021, and 2022 (NCI Omnibus R03 Clinical Trial Optional)

(PAR-20-052)

National Cancer Institute

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