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Liver Digest

A weekly update of PLRC happenings

March 14, 2019

PITTSBURGH LIVER RESEARCH CENTER
A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Alan Wells

REMINDER - Deadline for PLRC P&F applications is

tomorrow, March 15, at 5:00 p.m.

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Next Week's Seminars

Liver Seminar

Wed, March 20, noon-1:00 pm

1104 Scaife

Ariel E. Feldstein, MD

Professor of Pediatrics

Chief, Division of Pediatric Gastroenterology, Hepatology and Nutrition

UC San Diego School of Medicine

"NLRP3 Inflammasome in Liver Injury and Fibrosis"

Pizza will be provided.

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

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

Meeting Report:

Kobashigawa J, Dadhania D, Bhorade S, Adey D, Berger J, Bhat G, Budev M, Duarte-Rojo A, **Dunn M**, Hall S, Harhay MN, Johansen KL, Joseph S, Kennedy CC, Kransdorf E, Lentine KL, Lynch RJ, McAdams-DeMarco M, Nagai S, Olymbios M, Patel J, Pinney S, Schaenman J, Segev DL, Shah P, Singer LG, Singer JP, Sonnenday C, Tandon P, Tapper E, Tullius SG, Wilson M, Zamora M, Lai JC. Report from the American Society of Transplantation on frailty in solid organ transplantation. Am J Transplant. 2018 Dec 1. doi: 10.1111/ajt.15198. [Epub ahead of print] PubMed PMID: 30506632.

ABSTRACT

A consensus conference on frailty in kidney, liver, heart, and lung transplantation sponsored by the American Society of Transplantation (AST) and endorsed by the American Society of Nephrology (ASN), the American Society of Transplant Surgeons (ASTS), and the Canadian Society of Transplantation (CST) took place on February 11, 2018 in Phoenix, Arizona. Input from the transplant community through scheduled conference calls enabled wide discussion of current concepts in frailty, exploration of best practices for frailty risk assessment of transplant candidates and for management after transplant, and development of ideas for future research. A current understanding of frailty was compiled by each of the solid organ groups and is presented in this paper. Frailty is a common entity in patients with end-stage organ disease who are awaiting organ transplantation, and affects mortality on the waitlist and in the posttransplant period. The optimal methods by which frailty should be measured in each organ group are yet to be determined, but studies are underway. Interventions to reverse frailty vary among organ groups and appear promising. This conference achieved its intent to highlight the importance of frailty in organ transplantation and to plant the seeds for further discussion and research in this field.

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

Article Award:

Dr. Angus Thomson's group has been selected to receive a Vanguard award for the Best Basic Science Paper at the International Liver Transplantation Society Annual Congress. The Congress will be held in May in Toronto. Dr. David Geller also contributed to the study. Congratulations!

Toshimasa Nakao, Yoshihiro Ono, Helong Dai, Ryosuke Nakano, Angelica Perez-Gutierrez, Geoffrey Camirand, Hai Huang, **David A. Geller**, and **Angus W. Thomson**. (2019), DNAX Activating Protein of 12 kDa/Triggering Receptor Expressed on Myeloid Cells 2 Expression by Mouse and Human Liver Dendritic Cells: Functional Implications and Regulation of Liver Ischemia-Reperfusion Injury. Hepatology. doi:10.1002/hep.30334

ABSTRACT

Liver interstitial dendritic cells (DCs) have been implicated in the control of ischemia-reperfusion injury (IRI) and host immune responses following liver transplantation. Mechanisms underlying these regulatory functions of hepatic DCs remain unclear. We have shown recently that the transmembrane immunoadaptor DNAX-activating protein of 12 kDa (DAP12) negatively regulates mouse liver DC maturation and proinflammatory and immune stimulatory functions. Here, we used PCR analysis and flow cytometry to characterize expression of DAP12 and its associated triggering receptor, triggering receptor expressed on myeloid cells 2 (TREM2), by mouse and human liver DCs and other immune cells compared with DCs in other tissues. We also examined the roles of DAP12 and TREM2 and their expression by liver DCs in the regulation of liver IRI. Injury was induced in DAP12-/-, TREM2-/-, or wildtype (WT) mice by 1 hour of 70% clamping and quantified following 6 hours of reperfusion. Both DAP12 and TREM2 were coexpressed at comparatively high levels by liver DCs. Mouse liver DCs lacking DAP12 or TREM2 displayed enhanced levels of nuclear factor κB and costimulatory molecule expression. Unlike normal WT liver DCs, DAP12-/- liver DC failed to inhibit proliferative responses of activated T cells. In vivo, DAP12-/- and TREM2-/- mice exhibited enhanced IRI accompanied by augmented liver DC activation. Elevated alanine aminotransferase levels and tissue injury were markedly reduced by infusion of WT but not DAP12-/- DC. Conclusion: Our data reveal a close

association between DAP12 and TREM2 expression by liver DC and suggest that, by negatively regulating liver DC stimulatory function, DAP12 promotes their control of hepatic inflammatory responses; the DAP12/TREM2 signaling complex may represent a therapeutic target for control of acute liver injury/liver inflammatory disorders. (Hepatology 2019;0:1-15).

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

Original Article:

Qiao Y, Xu M, Tao J, Che L, Cigliano A, **Monga SP**, Calvisi DF, Chen X. Oncogenic potential of N-terminal deletion and S45Y mutant β-catenin in promoting hepatocellular carcinoma development in mice. BMC Cancer. 2018 Nov 12;18(1):1093. doi: 10.1186/s12885-018-4870-z. PubMed PMID: 30419856; PubMed Central PMCID: PMC6233269.

ABSTRACT

BACKGROUND: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death worldwide with limited treatment options. Mutation of β-catenin is one of the most frequent genetic events along hepatocarcinogenesis. β-catenin mutations can be in the form of point mutation or large N-terminal deletion. Studies suggested that different β-catenin mutations might have distinct oncogenic potential.

METHODS: We tested the oncogenic activity of β-cateninS45Y, one of the most frequent point mutations of β-catenin, and ΔN90-β-catenin, a form of β-catenin with a large N-terminal deletion, in promoting HCC development in mice. Thus, we co-expressed β-cateninS45Y or ΔN90-β-catenin together with c-Met into the mouse liver using hydrodynamic injection.

RESULTS: We found that both β-catenin mutations were able to induce

HCC formation in combination with c-Met at the same latency and efficiency. Tumors showed similar histological features and proliferation rates. However, immunohistochemistry showed predominantly nuclear staining of β-catenin in c-Met/ΔN90-β-catenin HCC, but membrane immunoreactivity in c-Met/β-cateninS45Y HCC. qRT-PCR analysis demonstrated that both ΔN90-β-catenin and β-cateninS45Y induced the same effectors, although at somewhat different levels. In cultured cells, both ΔN90-β-catenin and β-cateninS45Y were capable of inducing TCF/LEF reporter expression, promoting proliferation, and inhibiting apoptosis.

CONCLUSIONS: Our study suggests that β-cateninS45Y and ΔN90-β-catenin, in combination with the c-Met proto-oncogene, have similar oncogenic potential. Furthermore, nuclear staining of β-catenin does not always characterize β-catenin activity.

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

Original Article:
Krzysiak TC, Thomas L, Choi YJ, Auclair S, Qian Y, Luan S, Krasnow SM, Thomas LL, Koharudin LMI, **Benos PV**, Marks DL, Gronenborn AM, **Thomas G**. An Insulin-Responsive Sensor in the SIRT1 Disordered Region Binds DBC1 and PACS-2 to Control Enzyme Activity. Mol Cell. 2018 Dec 20;72(6):985-998.e7. doi: 10.1016/j.molcel.2018.10.007. Epub 2018 Nov 8. PubMed PMID: 30415949; PubMed Central PMCID: PMC6309500.

ABSTRACT
Current models of SIRT1 enzymatic regulation primarily consider the effects of fluctuating levels of its co-substrate NAD+, which binds to the stably folded catalytic domain. By contrast, the roles of the sizeable disordered N- and C-terminal regions of SIRT1 are

largely unexplored. Here we identify an insulin-responsive sensor in the SIRT1 N-terminal region (NTR), comprising an acidic cluster (AC) and a 3-helix bundle (3HB), controlling deacetylase activity. The allosteric assistor DBC1 removes a distal N-terminal shield from the 3-helix bundle, permitting PACS-2 to engage the acidic cluster and the transiently exposed helix 3 of the 3-helix bundle, disrupting its structure and inhibiting catalysis. The SIRT1 activator (STAC) SRT1720 binds and stabilizes the 3-helix bundle, protecting SIRT1 from inhibition by PACS-2. Identification of the SIRT1 insulin-responsive sensor and its engagement by the DBC1 and PACS-2 regulatory hub provides important insight into the roles of disordered regions in enzyme regulation and the mode by which STACs promote metabolic fitness.

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

Original Article:

Shinji Furuya, Joseph A Cichocki, Kranti Konganti, Kostiantyn Dreval, Takeki Uehara, Yuuki Katou, Hisataka Fukushima, Hiroshi Kono, Igor P Pogribny, Josepmaria Argemi, **Ramon Bataller**, Ivan Rusyn; Histopathological and Molecular Signatures of a Mouse Model of Acute-on-Chronic Alcoholic Liver Injury Demonstrate Concordance With Human Alcoholic Hepatitis, Toxicological Sciences, kfy292, **https://doi.org/10.1093/toxsci/kfy292**.

ABSTRACT

Human alcoholic hepatitis (AH) carries a high mortality rate. AH is an acute-on-chronic form of liver injury characterized by hepatic steatosis, ballooned hepatocytes, neutrophil infiltration, and pericellular fibrosis. We aimed to study the pathogenesis of AH in an animal model which combines chronic hepatic fibrosis with intragastric alcohol administration. Adult male C57BL6/J mice were

treated with CCl4 (0.2 ml/kg, 2×weekly by intraperitoneal injections for 6 weeks) to induce chronic liver fibrosis. Then, ethyl alcohol (up to 25 g/kg/day for 3 weeks) was administered continuously to mice via a gastric feeding tube, with or without one-half dose of CCl4. Liver and serum markers and liver transcriptome were evaluated to characterize acute-on-chronic-alcoholic liver disease in our model. CCl4 or alcohol treatment alone induced liver fibrosis or steatohepatitis, respectively, findings that were consistent with expected pathology. Combined treatment resulted in a marked exacerbation of liver injury, as evident by the development of inflammation, steatosis, and pericellular fibrosis, pathological features of human AH. E. coli and Candida were also detected in livers of mice cotreated with CCl4 and alcohol, indicating pathogen translocation from gut to liver, similar to human AH. Importantly, liver transcriptomic changes specific to combined treatment group demonstrated close concordance with pathways perturbed in patients with severe AH. Overall, mice treated with CCl4 and alcohol displayed key molecular and pathological characteristics of human AH—pericellular fibrosis, increased hepatic bacterial load, and dysregulation of the same molecular pathways. This model may be useful for developing therapeutics for AH.

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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