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Liver Digest

A weekly update of PLRC happenings

June 20, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Sadeesh Ramakrishnan

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Upcoming Seminar

Liver Seminar:
Mon, 06/24/2019
4:00 p.m. - 5:00 p.m.
Scaife Hall - Lecture Room 6

Provost Ann E. Cudd cordially invites you to an Inaugural Lecture by
Shari S. Rogal, MD, MPH
John J. Fung/Astellas Pharma US Assistant Professor of Transplant Surgery
School of Medicine

"Using Implementation Science to Improve Care for Patients with Chronic Liver Disease"

https://calendar.pitt.edu/event/using_implementation_science_to_improve_care_for_patients_with_chronic_liver_disease#.XQj1nrxKg-U

Faculty Highlights

Original Article:
Coudriet GM, Stoops J, Orr AV, Bhushan B, Koral K, Lee S, Previte DM, **Dong HH**, **Michalopoulos GK**, **Mars WM**, Piganelli JD. A Noncanonical Role for Plasminogen Activator Inhibitor Type 1 in Obesity-Induced Diabetes. Am J Pathol. 2019 May 2. pii: S0002-9440(18)30877-0. doi: 10.1016/j.ajpath.2019.04.004. [Epub ahead of print] PubMed PMID: 31054988.

ABSTRACT
Obesity is a major risk factor for type 2 diabetes because of chronic hepatic inflammation and resultant insulin resistance. Hepatocyte growth factor (HGF)

is responsible for resetting hepatic homeostasis after injury following activation by urokinase-type plasminogen activator (u-PA; encoded by the PLAU gene). Plasminogen activator inhibitor type-1 (PAI-1; encoded by the SERPINE1 gene), a u-PA inhibitor and antifibrinolytic agent, is often elevated in obesity and is linked to cardiovascular events. We hypothesized that, in addition to its role in preventing fibrinolysis, elevated PAI-1 inhibits HGF's activation by u-PA and the resultant anti-inflammatory and hepatoprotective properties. Wild-type and PAI-1 knockout (KO) mice on a high-fat diet both became significantly heavier than lean controls; however, the obese KO mice demonstrated improved glucose metabolism compared with wild-type mice. Obese KO mice also exhibited an increase in conversion of latent single-chain HGF to active two-chain HGF, coinciding with an increase in the phosphorylation of HGF receptor, MET, as well as dampened inflammation. These results strongly suggest that, in addition to its other functions, PAI-mediated inhibition of HGF activation prohibits the resolution of inflammation in the context of obesity-induced type 2 diabetes.

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

Original Article:

Rachakonda V, Argemi J, **Borhani AA**, **Bataller R**, Tevar A, **Behari J**. Reduced Serum Sphingolipids Constitute a Molecular Signature of Malnutrition in Hospitalized Patients With Decompensated Cirrhosis. Clin Transl Gastroenterol. 2019 Mar;10(3):e00013. doi: 10.14309/ctg.0000000000000013. PubMed PMID: 30908309; PubMed Central PMCID: PMC6445606.

ABSTRACT

INTRODUCTION: Malnutrition is a leading cause of morbidity and mortality in cirrhosis. Although multiple noninvasive measures of nutritional status have been studied, no consensus exists for early identification of malnutrition in cirrhosis. Serum metabolomics offers a novel approach for identifying biomarkers in multiple disease states. To characterize alterations in metabolic pathways associated with malnutrition in hospitalized cirrhotic patients and to identify biomarkers for disease prognosis.

METHODS: In this cross-sectional, observational cohort study, 51 hospitalized cirrhotic patients were classified as malnourished (42.3%) or nourished (57.7%) based on low mid-arm muscle circumference and dominant handgrip strength. Anthropometric measurements and computed tomography body composition

analysis were performed. Serum was collected after overnight fasting for unbiased metabolomics analysis.

RESULTS: Malnourished cirrhotic patients exhibited mild reductions in skeletal muscle index, with more marked reductions in visceral fat index. Seventy-one biochemicals were significantly altered in malnourished subjects. The serum metabolite profile was significantly different between nourished and malnourished cirrhotic patients. Pathway analysis demonstrated that only sphingolipid metabolic pathways were significantly enriched in altered metabolites. Hierarchical clustering revealed that sphingolipid metabolites clustered into nourished and malnourished cohorts. Spearman analysis demonstrated multiple statistically significant correlations between sphingolipid species and Model for End-Stage Liver Disease-Sodium. Using logistic regression, we identified 8 sphingolipids that were significantly associated with malnutrition after controlling for Model for End-Stage Liver Disease-Sodium, age, and gender.

CONCLUSIONS: Malnutrition in hospitalized cirrhotic patients is characterized by reductions in multiple sphingolipid species. Dysregulated sphingolipid metabolism may be involved in the pathophysiology of malnutrition in cirrhosis and potentially serve as a biomarker of nutritional status in this population.

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

Original Article:

Marina Ruiz de Galarreta, Erin Bresnahan, Pedro Molina-Sanchez, Katherine E Lindblad, Barbara Maier, Daniela Sia, Marc Puigvehi, Verónica Miguela, Maria Casanova-Acebes, Maxime Dhainaut, Carlos Villacorta-Martin, **Aatur D Singhi**, Akshata Moghe, Johann von Felden, Lauren Tal Grinspan, Shuang Wang, Alice O Kamphorst, **Satdarshan P Monga**, Brian D Brown, Augusto Villanueva, Josep M Llovet, Miriam Merad and Amaia Lujambio. 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 hepatocellular carcinoma (HCC) patients. However, what determines resistance to anti-PD-1 therapies is unclear. We created a novel genetically-engineered

mouse model of HCC that enables interrogating how different genetic alterations affect immune surveillance and response to immunotherapies. Expression of exogenous antigens in MYC;p53-/- HCCs led to T cell-mediated immune surveillance, which was accompanied by decreased tumor formation and increased survival. Some antigen-expressing MYC;p53-/- HCCs escaped the immune system by upregulating 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.

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

Review Article:

Barbosa ACS, Feng Y, Yu C, Huang M, **Xie W**. Estrogen sulfotransferase in the metabolism of estrogenic drugs and in the pathogenesis of diseases. Expert Opin Drug Metab Toxicol. 2019 Apr;15(4):329-339. doi: 10.1080/17425255.2019.1588884. Epub 2019 Mar 18. PubMed PMID: 30822161; PubMed Central PMCID: PMC6428602.

ABSTRACT

Biotransformation is important in the metabolism of endobiotics and xenobiotics. This process comprises the activity of phase I and phase II enzymes. Estrogen sulfotransferase (SULT1E1 or EST) is a phase II conjugating enzyme that belongs to the family of cytosolic sulfotransferases. The expression of SULT1E1 can be detected in many tissues, including the liver. SULT1E1 catalyzes the transfer of a sulfate group from 3'-phosphoadenosine-5'-phosphosulfate (PAPS) to any available hydroxyl group in estrogenic molecules. The substrates of SULT1E1 include the endogenous and synthetic estrogens. Upon SULT1E1-mediated sulfation, the hydrosolubility of estrogens increases, preventing the binding between the sulfated estrogens and the estrogen receptor (ER). This sulfated state of the estrogens is not irreversible, as the steroid sulfatase (STS) can convert sulfoconjugated estrogens to free estrogens. The expression of SULT1E1 is inducible by several diseases that involve tissue inflammation, such as type 2 diabetes, sepsis, and ischemia-reperfusion injury. Areas covered: This systematic literature review aims to

summarize the role of SULT1E1 in the metabolism of estrogenic drugs and xenobiotics, and the role of SULT1E1 in the pathogenesis of several diseases, including cancer, metabolic disease, sepsis, liver injury, and cystic fibrosis. Meanwhile, ablation or pharmacological inhibition of SULT1E1 can affect the outcomes of the aforementioned diseases. Expert opinion: In addition to its role in metabolizing estrogenic drugs, SULT1E1 is unexpectedly being unveiled as a mediator for the disease effect on estrogen metabolism and homeostasis. Meanwhile, because the expression and activity of SULT1E1 can affect the outcome of diseases, the same sulfotransferase and the reversing enzymes STS can be potential therapeutic targets to prevent or manage diseases. Accumulating evidence suggest that the physiological and pathophysiological effects of SULT1E1 can be estrogen-independent and it is necessary to elucidate what other possible substrates may be recognized by the enzyme. Moreover, human studies are paramount to confirm the human relevance of the animal studies.

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

Original Article:
Schmelzer E, McKeel DT, **Gerlach JC**. Characterization of Human Mesenchymal Stem Cells from Different Tissues and Their Membrane Encasement for Prospective Transplantation Therapies. Biomed Res Int. 2019 Mar 3;2019:6376271. doi: 10.1155/2019/6376271. eCollection 2019. PubMed PMID: 30941369; PubMed Central PMCID: PMC6421008.

ABSTRACT
Human mesenchymal stem cells can be isolated from various organs and are in studies on therapeutic cell transplantation. Positive clinical outcomes of transplantations have been attributed to both the secretion of cytokines and growth factors as well as the fusion of donor cells with that of the host. We compared human mesenchymal stem cells from six different tissues for their transplantation-relevant potential. Furthermore, for prospective allogenic transplantation we developed a semipermeable hollow-fiber membrane enclosure, which would prevent cell fusion, would provide an immune barrier, and would allow for easy removal of donor cells from patients after recovery. We investigated human mesenchymal stem cells from adipose tissue, amniotic tissue, bone marrow, chorionic tissue, liver, and umbilical cord. We compared their multilineage differentiation potential, secretion of growth factors, and the expression of genes and surface markers. We found that although the

expression of typical mesenchymal stem cell-associated gene THY1 and surface markers CD90 and CD73 were mostly similar between mesenchymal stem cells from different donor sites, their expression of lineage-specific genes, secretion of growth factors, multilineage differentiation potential, and other surface markers were considerably different. The encasement of mesenchymal stem cells in fibers affected the various mesenchymal stem cells differently depending on their donor site. Conclusively, mesenchymal stem cells isolated from different tissues were not equal, which should be taken into consideration when deciding for optimal sourcing for therapeutic transplantation. The encasement of mesenchymal stem cells into semipermeable membranes could provide a physical immune barrier, preventing cell fusion.

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

Funding Opportunity

"Clinical Trials" on a Chip: Tissue Chips to Inform Clinical Trial Design and Implementation in Precision Medicine (UG3/UH3 - Clinical Trial Not Allowed)

(RFA-TR-19-014)
National Center for Advancing Translational Sciences
National Cancer Institute
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institute of Dental and Craniofacial Research

Our mailing address is:

Pittsburgh Liver Research Center
200 Lothrop St. | Pittsburgh, PA 15261