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Liver Digest

A weekly update of PLRC happenings

November 27, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Silvia Liu

In this issue

Next Week's Seminar

PLRC Seminar Series

Tue, 12/03/2019

12:00 to 1:00 pm

S123 BST

Scott Morley, MBA

Coulter Program Director

Entrepreneur-in-Residence, Innovation Institute

From Bench, to Bedside, to Business: Commercializing Your Medtech Innovation

Pizza will be provided.

The full schedule of Enrichment activities is posted on **https://www.livercenter.pitt.edu/events**.

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:

Ashokkumar C, Green M, Soltys K, Michaels M, Mazariegos G, Reyes-Mugica M, Higgs BW, Spishock B, Zaccagnini M, Sethi P, Rzempoluch A, Kepler A, Kachmar P, Remaley L, Winnier J, Jones K, Moir K, Fazzolare T, Jenkins K, Hartle T, Falik R, Ningappa M, Bond G, Khanna A, Ganoza A, Sun Q, **Sindhi R**. CD154-expressing CMV-specific T cells associate with freedom from DNAemia and may be protective in seronegative recipients after liver or intestine transplantation. Pediatr Transplant. 2019 Oct 27:e13601. doi: 10.1111/petr.13601. PubMed PMID: 31657119.

ABSTRACT

Cell-mediated immunity to CMV, if known, could improve antiviral drug therapy in at-risk children and young adults with LT and IT. Host immunity has been measured with CMV-specific T cells, which express IFNγ, but not those which express CD154, a possible substitute for IFNγ. CMV-specific CD154+ T cells and their subsets were measured with flow cytometry after stimulating PBL from recipient blood samples with an overlapping peptide mix of CMV-pp65 antigen for up to 6 hours. CMV-specific CD154+ T cells co-expressed IFNγ in PBL from three healthy adults and averaged 3.8% (95% CI 3.2%-4.4%) in 40 healthy adults. CMV-specific T cells were significantly lower in 19 CMV DNAemic LT or IT recipients, compared with 126 non-DNAemic recipients, 1.3% (95% CI 0.8-1.7) vs 4.1 (95%

CI 3.6-4.6, P < .001). All T-cell subsets demonstrated similar between-group differences. In logistic regression analysis of 46 training set samples, 12 with DNAemia, all obtained between days 0 and 60 from transplant, CMV-specific T-cell frequencies ≥1.7% predicted freedom from DNAemia with NPV of 93%. Sensitivity, specificity, and PPV were 83%, 74%, and 53%, respectively. Test performance was replicated in 99 validation samples. In 32 of 46 training set samples, all from seronegative recipients, one of 19 recipients with CMV-specific T-cell frequencies ≥1.7% experienced DNAemia, compared with 8 of 13 recipients with frequencies <1.7% (P = .001). CMV-specific CD154+ T cells are associated with freedom from DNAemia after LT and IT. Among seronegative recipients, CMV-specific T cells may protect against the development of CMV DNAemia.

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

Original Article:

Fuhrman DY, Kellum JA, Joyce EL, Miyashita Y, Mazariegos GV, Ganoza A, **Squires JE**. The use of urinary biomarkers to predict acute kidney injury in children after liver transplant. Pediatr Transplant. 2019 Oct 25:e13608. doi: 10.1111/petr.13608. PubMed PMID: 31652022.

BACKGROUND: AKI after pediatric liver transplantation is associated with increased morbidity and mortality. The role of urinary biomarkers for the prediction of AKI in pediatric patients after liver transplantation has not been previously reported. The primary objective of this prospective pilot study was to determine the predictive capabilities of urinary KIM-1, NGAL, TIMP-2, and IGFBP7 for diagnosing AKI.

METHODS: Sixteen children undergoing liver transplantation were

enrolled in the study over a 19-month time period. The Kidney Disease Improving Outcomes criteria for urine output and serum creatinine were used to define AKI. Predictive ability was evaluated using the area under the curve obtained by ROC analysis.

RESULTS: AKI occurred in 6 (37.5%) of the patients between 2 and 4 days after transplant. There were no differences in any of the biomarkers prior to transplant. When obtained within 6 hours after transplant, the area under the ROC curve for predicting AKI was 0.758 (95% CI: 0.458-1.00) for KIM-1, 0.900 (95% CI: 0.724-1.00) for NGAL, and 0.933 (95% CI: 0.812-1.00) for the product of TIMP-2 and IGFBP7 ([TIMP-2]·[IGFBP7]).

CONCLUSIONS: Our results show that both NGAL and [TIMP-2]·[IGFBP7] provide significant discrimination for AKI risk following liver transplant in children. Larger studies are needed to determine the optimal time point for measuring these biomarkers and to validate our findings.

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

Original Article:
Zhu Y, Gu L, Lin X, Liu C, Lu B, Cui K, Zhou F, Zhao Q, **Prochownik EV**, Fan C, Li Y. Dynamic Regulation of ME1 Phosphorylation and Acetylation Affects Lipid Metabolism and Colorectal Tumorigenesis. Mol Cell. 2019 Nov 5. pii: S1097-2765(19)30793-2. doi: 10.1016/j.molcel.2019.10.015. PubMed PMID: 31735643.

ABSTRACT
PGAM5 is a mitochondrial serine/threonine phosphatase that regulates multiple metabolic pathways and contributes to tumorigenesis in a poorly understood manner. We show here that PGAM5 inhibition attenuates lipid metabolism and colorectal

tumorigenesis in mice. PGAM5-mediated dephosphorylation of malic enzyme 1 (ME1) at S336 allows increased ACAT1-mediated K337 acetylation, leading to ME1 dimerization and activation, both of which are reversed by NEK1 kinase-mediated S336 phosphorylation. SIRT6 deacetylase antagonizes ACAT1 function in a manner that involves mutually exclusive ME1 S336 phosphorylation and K337 acetylation. ME1 also promotes nicotinamide adenine dinucleotide phosphate (NADPH) production, lipogenesis, and colorectal cancers in which ME1 transcripts are upregulated and ME1 protein is hypophosphorylated at S336 and hyperacetylated at K337. PGAM5 and ME1 upregulation occur via direct transcriptional activation mediated by β-catenin/TCF1. Thus, the balance between PGAM5-mediated dephosphorylation of ME1 S336 and ACAT1-mediated acetylation of K337 strongly influences NADPH generation, lipid metabolism, and the susceptibility to colorectal tumorigenesis.

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

Original Article:

Wang L, **Sparacino-Watkins CE**, Wang J, Wajih N, Varano P, Xu Q, Cecco E, Tejero J, Soleimani M, Kim-Shapiro DB, Gladwin MT. Carbonic Anhydrase II Does Not Regulate Nitrite Dependent Nitric Oxide Formation and Vasodilation. Br J Pharmacol. 2019 Oct 28. doi: 10.1111/bph.14887. PubMed PMID: 31658361.

ABSTRACT

BACKGROUND AND PURPOSE: Although it has been reported that bovine CAII is capable of generating NO from nitrite, the function and mechanism of CAII in nitrite-dependent NO formation and vascular responses remain controversial. We tested the hypothesis that CAII catalyzes NO formation from nitrite and contributes to nitrite dependent inhibition of platelet activation and vasodilation.

EXPERIMENTAL APPROACH: The role of CAII in enzymatic NO generation was investigated by measuring NO formation from the reaction of isolated human and bovine CAII with nitrite using NO photolysis-chemiluminescence. A CAII-deficient mouse model was used to determine the role of CAII in red blood cell mediated nitrite reduction and vasodilation.

KEY RESULTS: We found that the commercially available purified bovine CAII exhibited limited and non-enzymatic NO-generating reactivity in the presence of nitrite with or without addition of the CA inhibitor dorzolamide; the NO formation was eliminated with purification of the enzyme. There was no significant detectable NO production from the reaction of nitrite with recombinant human CAII. Using a CAII-deficient mouse model, there were no measurable changes in nitrite-dependent vasodilation in isolated aorta rings and in vivo in CAII-/- , CAII+/- and wide type mice. Moreover, deletion of the CAII gene in mice did not block nitrite reduction by red blood cells and the nitrite-NO dependent inhibition of platelet activation.

CONCLUSION AND IMPLICATIONS: These studies suggest that human, bovine and mouse CAII are not responsible for nitrite dependent NO formation in red blood cells, aorta or the systemic circulation.

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