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Liver Digest

A weekly update of PLRC happenings

August 29, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Marlies Meisel

In this issue

PLRC Meet and Greet

September 12, 2019
4:30-7:30 p.m.
University Club
Dinner Reception included.
Full program forthcoming.

Fall 2019 Liver Seminar Schedule

Liver Seminar - Dr. Gregory Gores
Wed, 09/11/2019
12:00 to 1:00 pm
1104 Scaife

Gregory J. Gores, MD

Professor of Medicine & Physiology
Executive Dean for Research, Mayo Foundation for Medical Education and Research
Mayo Clinic, Rochester, Minnesota

"Cholangiocarcinoma: Mice to Human"

Department of Pathology Seminar, co-sponsored by PLRC

Liver Seminar - Dr. Drew Feranchak

Wed, 09/25/2019
12:00 to 1:00 pm
1104 Scaife

Andrew Feranchak, MD
Chief, Division of Pediatric Gastroenterology, Hepatology, and Nutrition
Children's Hospital of Pittsburgh

Targeting Non-CFTR C1- Channels for the Treatment of Cystic Fibrosis Liver Disease

Department of Pathology Seminar, co-sponsored by PLRC

PLRC Seminar Series - Dr. Valerie Gouon-Evans

Tue, 10/01/2019
12:00 to 1:00 pm
S120 BST

Valerie Gouon-Evans, Pharm.D., Ph.D.
Associate Professor
Department of Medicine, Section of Gastroenterology
Center for Regenerative Medicine CReM
Boston University School of Medicine and Boston Medical Center

Title TBA

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

Pizza will be provided.

PLRC Seminar Series - Dr. Josep Llovet

Tue, 10/15/2019
12:00 to 1:00 pm
S120 BST

Josep Llovet, MD
Professor of Medicine

Founder and Director of the Liver Cancer Program
Mount Sinai School of Medicine

Molecular Targeted Therapies in HCC

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

Pizza will be provided.

Liver Seminar - Dr. Al Sirica

October 23, 2019
12:00 to 1:00 pm
1104 Scaife

Alphonse E. Sirica, PhD

Professor of Pathology, Division of Cellular and Molecuar Pathogenesis
Virginia Commonwealth University School of Medicine

TGF-β Periostin, and Mesothelin in Intrahepatic Cholangiocarcinoma: Pathological Insights and Translational Implications

Pathology Department Seminar, co-sponsored by PLRC

PLRC Seminar Series - Dr. Tatiana Kisseleva

Tue, 11/19/2019
12:00 to 1:00 pm
S120 BST

Tatiana Kisseleva, MD, PhD

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

Title TBA

PLRC Seminar Series - Dr. Takanori Takebe

Tue, 12/17/2019
12:00 to 13:00

S120 BST

Takanori Takebe, MD
Assistant Professor, University of Cincinnati, Department of Pediatrics
Associate Professor, Department of Regenerative Medicine, Yokohama City University, Japan

Title TBA

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:

Mandel J, Wang H, Normolle DP, Chen W, Yan Q, **Lucas PC, Benos PV, Prochownik EV**. Expression patterns of small numbers of transcripts from functionally-related pathways predict survival in multiple cancers. BMC Cancer. 2019 Jul 12;19(1):686. doi: 10.1186/s12885-019-5851-6. PubMed PMID: 31299925; PubMed Central PMCID: PMC6626418.

ABSTRACT
BACKGROUND: Genetic profiling of cancers for variations in copy number, structure or expression of certain genes has improved diagnosis, risk-stratification and therapeutic decision-making. However the tumor-restricted nature of these changes limits their application to certain cancer types or sub-types. Tests with broader prognostic capabilities are lacking.

METHODS: Using RNAseq data from 10,227 tumors in The Cancer Genome Atlas (TCGA), we evaluated 212 protein-coding transcripts from 12 cancer-related pathways. We employed t-distributed stochastic neighbor embedding (t-SNE) to identify expression pattern difference among each pathway's transcripts. We have previously used t-SNE to show that survival in some cancers correlates with expression patterns of transcripts encoding ribosomal proteins and enzymes for cholesterol biosynthesis and fatty acid oxidation.

RESULTS: Using the above 212 transcripts, t-SNE-assisted transcript pattern profiling identified patient cohorts with significant survival differences in

30 of 34 different cancer types comprising 9350 tumors (91.4% of all TCGA cases). Small subsets of each pathway's transcripts, comprising no more than 50-60 from the original group, played particularly prominent roles in determining overall t-SNE patterns. In several cases, further refinements in long-term survival could be achieved by sequential t-SNE profiling with two pathways' transcripts, by a combination of t-SNE plus whole transcriptome profiling or by employing t-SNE on immuno-histochemically defined breast cancer subtypes. In two cancer types, individuals with Stage IV disease at presentation could be readily subdivided into groups with highly significant survival differences based on t-SNE-based tumor sub-classification.

CONCLUSIONS: t-SNE-assisted profiling of a small number of transcripts allows the prediction of long-term survival across multiple cancer types.

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

Original Article:

Lamparello AJ, Namas RA, Schimunek L, Cohen M, El-Dehaibi F, Yin J, Barclay D, **Zamora R, Billiar TR, Vodovotz Y**. An Aging-Related Single-Nucleotide Polymorphism is Associated with Altered Clinical Outcomes and Distinct Inflammatory Profiles in Aged Blunt Trauma Patients. Shock. 2019 Jul 16. doi: 10.1097/SHK.0000000000001411. PubMed PMID: 31318836.

ABSTRACT

The contribution of individual genetic determinants of aging to the adverse clinical outcomes and altered inflammation mediator networks characteristic of aged trauma patients is unknown. The AA genotype of the aging-related single-nucleotide polymorphism (SNP) rs2075650 in TOMM40 has been associated with longevity, while the AG and GG genotypes are associated with an increased risk of Alzheimer's disease. Here, we studied the effect of rs2075650 on clinical outcomes and dynamic biomarker patterns after traumatic injury. Genomic DNA was obtained from blunt trauma patients admitted to the ICU and examined for 551,839 SNPs using an Illumina microarray kit. Plasma was sampled from each patient three times within the first 24hours and daily from day 1 to 7 then assayed for 31 biomarkers using Luminex. Aged patients (65-90 years) were segregated into AA (n=77) and AG/GG (n=17) genotypes. Additional comparisons were made with matched groups of young patients (18-30 years), controlling for

injury severity score (ISS) and sex ratio, and also segregated into AA (n=56) and AG/GG (n=19) genotypes. Aged patients with the AA genotype had a significantly lower requirement for ventilation and fewer days on mechanical ventilation, as well as significantly higher levels of one mediator and lower levels of two mediators. Dynamic Bayesian Network inference revealed IL-23 as a central node in each network regardless of age or genotype, with MIG and IP-10 also as key mediators in the networks of the aged patients. These findings suggest that an aging-related SNP, rs2075650, may influence clinical outcomes and inflammation networks in aged patients following blunt trauma, and thus may serve as a predictive outcome biomarker in the setting of polytrauma.

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

Original Article:

Ezzelarab MB, Perez-Gutierrez A, **Humar A**, Wijkstrom M, Zahorchak AF, Lu-Casto L, Wang YC, Wiseman RW, Minervini M, **Thomson AW.** Preliminary assessment of the feasibility of autologous myeloid-derived suppressor cell infusion in non-human primate kidney transplantation. Transpl Immunol. 2019 Jul 19:101225. doi: 10.1016/j.trim.2019.101225. PubMed PMID: 31330261.

ABSTRACT

Myeloid-derived suppressor cells (MDSC) are a heterogenous population of immunosuppressive myeloid cells now considered important immune regulatory cells in diverse clinical conditions, including cancer, chronic inflammatory disorders and transplantation. In rodents, MDSC administration can inhibit graft-versus-host disease lethality and enhance organ or pancreatic islet allograft survival. There is also evidence, however, that under systemic inflammatory conditions, adoptively-transferred MDSC can rapidly lose their suppressive function. To our knowledge, there are no reports of autologous MDSC administration to either human or clinically-relevant non-human primate (NHP) transplant recipients. Monocytic (m) MDSC have been shown to be more potent suppressors of T cell responses than other subsets of MDSC. Following their characterization in rhesus macaques, we have conducted a preliminary analysis of the feasibility and preliminary efficacy of purified mMDSC infusion into MHC-mismatched rhesus kidney allograft recipients. The graft recipients were treated with rapamycin and the high affinity variant of the T cell co-stimulation blocking agent cytotoxic T lymphocyte antigen 4 Ig (Belatacept) that targets the B7-CD28 pathway. Graft survival and histology were not affected by infusions of autologous, leukapheresis product-derived

mMDSC on days 7 and 14 post-transplant (cumulative totals of 3.19 and 1.98 × 106 cells/kg in n = 2 recipients) compared with control monkeys that did not receive MDSC (n = 2). Sequential analyses of effector T cell populations revealed no differences between the groups. While these initial findings do not provide evidence of efficacy under the conditions adopted, further studies in NHP, designed to ascertain the appropriate mMDSC source and dose, timing and anti-inflammatory/immunosuppressive agent support are likely to prove instructive regarding the therapeutic potential of MDSC in organ transplantation.

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

Original Article:

Billiar IM, Guardado J, Abdul-Malak O, **Vodovotz Y, Billiar TR**, Namas RA. Elevations in Circulating sST2 Levels Are Associated With In-hospital Mortality and Adverse Clinical Outcomes After Blunt Trauma. J Surg Res. 2019 Jul 3;244:23-33. doi: 10.1016/j.jss.2019.05.057. PubMed PMID: 31279260.

ABSTRACT

BACKGROUND: Soluble suppression of tumorigenicity 2 (sST2), a decoy receptor for interleukin (IL)-33, has emerged as a novel biomarker in various disease processes. Recent studies have elucidated the role of the sST2/IL-33 complex in modulating the balance of Th1/Th2 immune responses after tissue stress. However, the role of sST2 as a biomarker after traumatic injury remains unclear. To address this, we evaluated serum sST2 correlations with mortality and in-hospital adverse outcomes as endpoints in blunt trauma patients.

METHODS: We retrospectively analyzed clinical and biobank data of 493 blunt trauma victims 472 survivors (mean age: 48.4 ± 0.87; injury severity score [ISS]: 19.6 ± 0.48) and 19 nonsurvivors (mean age: 58.8 ± 4.5; ISS: 23.3 ± 2.1) admitted to the intensive care unit. Given the confounding impact of age on the inflammatory response, we derived a propensity-matched survivor subgroup (n = 19; mean age: 59 ± 3; ISS: 23.4 ± 2) using an IBM SPSS case-control matching algorithm. Serial blood samples were obtained from all patients (3 samples within the first 24 h and then once daily from day [D] 1 to D5 after injury). sST2 and twenty-nine inflammatory biomarkers were assayed using enzyme-linked immunosorbent assay and Luminex, respectively. Two-way analysis of variance on ranks was used to compare groups ($P < 0.05$). Spearman rank correlation was performed to determine the association of circulating

sST2 levels with biomarker levels and in-hospital clinical outcomes.

RESULTS: Circulating sST2 levels of the nonsurvivor cohort were statistically significantly elevated at 12 h after injury and remained elevated up to D5 when compared either to the overall 472 survivor cohort or a matched 19 survivor subcohort. Admission sST2 levels obtained from the first blood draw after injury in the survivor cohort correlated positively with admission base deficit (correlation coefficient [CC] = 0.1; P = 0.02), international normalized ratio (CC = 0.1, P = 0.03), ISS (CC = 0.1, P = 0.008), and the average Marshall multiple organ dysfunction score between D2 and D5 (CC = 0.1, P = 0.04). Correlations with ISS revealed a positive correlation of ISS with plasma sST2 levels across the mild ISS (CC = 0.47, P < 0.001), moderate ISS (CC = 0.58, P < 0.001), and severe ISS groups (CC = 0.63, P < 0.001). Analysis of biomarker correlations in the matched survivor group over the initial 24 h after injury showed that sST2 correlates strongly and positively with IL-4 (CC = 0.65, P = 0.002), IL-5 (CC = 0.57, P = 0.01), IL-21 (CC = 0.52, P = 0.02), IL-2 (CC = 0.51, P = 0.02), soluble IL-2 receptor-α (CC = 0.5, P = 0.02), IL-13 (CC = 0.49, P = 0.02), and IL-17A (CC = 0.48, P = 0.03). This was not seen in the matched nonsurvivor group. sST2/IL-33 ratios were significantly elevated in nonsurvivors and patients with severe injury based on ISS ≥ 25.

CONCLUSIONS: Elevations in serum sST2 levels are associated with poor clinical trajectories and mortality after blunt trauma. High sST2 coupled with low IL-33 associates with severe injury, mortality, and worse clinical outcomes. These findings suggest that sST2 could serve as an early prognostic biomarker in trauma patients and that sustained elevations of sST2 could contribute to a detrimental suppression of IL-33 bioavailability in patients with high injury severity.

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

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