Liver Digest

A weekly update of PLRC happenings

September 19, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Patrick McKiernan

In this issue

- Funding Opportunities

Next Week's Seminars

Liver Seminar - Dr. Drew Feranchak

Wed, 09/25/2019

12:00 to 1:00 p.m.

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

Liver Seminar - Dr. David Thomas

Thu, 09/26/2019

4:00 p.m.

1103 Scaife

David L. Thomas, MD, MPH

Chief of the Division of Infectious Diseases

Stanhope Bayne Jones Professor

Department of Medicine

Johns Hopkins University School of Medicine

"Global Elimination of Hepatitis"

Infectious Diseases Grand Rounds special seminar sponsored by the Department of Medicine, Division of Infectious Diseases

This Department of Medicine Special Seminar is hosted by John W. Mellors, MD, chief, Division of Infectious Diseases, Professor for Global Elimination of HIV and AIDS, and professor of medicine, School of Medicine.

PLRC Meet and Greet

It was very nice to see so many of you at last week's Meet & Greet! Just a few quick follow-ups from the meeting:

1. Several of the Core leaders have graciously agreed to have their presentation slides (**please click here**) distributed to the PLRC members. Our thanks to all the presenters!
2. The link to the form for requesting services from the Genomics & Systems Biology Core is: **https://forms.gle/srirU73i2Kdednr19**
3. The NIH policy on acknowledging the PLRC P30 grant:

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "**Research reported in this publication was supported by the National Institute Of Diabetes And Digestive And Kidney Diseases of the National Institutes of Health under Award Number P30DK120531. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.**" Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Grant Award:

Congratulations to Dr. Wen Xie, Chair of the Department of Pharmaceutical Sciences, on being one of six scientists to receive an NIEHS Revolutionizing Innovative, Visionary Environmental health Research (RIVER) Award. Dr. Ramon Bataller is a collaborator on the study.

For more details on the study, please see the University of Pittsburgh Department of Pharmacy announcement (**available here)**, and the NIH announcement of the awards (**available here)**.

Original Article:

Esteban-Vives R, Ziembicki J, Choi MS, Thompson RL, Schmelzer E, **Gerlach JC**.

Isolation and Characterization of a Human Fetal Mesenchymal Stem Cell Population: Exploring the Potential for Cell Banking in Wound Healing Therapies. Cell Transplant. 2019 Aug 13:963689718817524. doi: 10.1177/0963689718817524. PubMed PMID: 31407589.

ABSTRACT

Various cell-based therapies are in development to address chronic and acute skin wound healing, for example for burns and trauma patients. An off-the-shelf source of allogeneic dermal cells could be beneficial for innovative therapies accelerating the healing in extensive wounds where the availability of a patient's own cells is limited. Human fetal-derived dermal fibroblasts (hFDF) show high in vitro division rates, exhibit low immunological rejection properties, and present scarless wound healing in the fetus, and previous studies on human fetal tissue-derived cell therapies have shown promising results on tissue repair. However, little is known about cell lineage stability and cell differentiation during the cell expansion process, required for any potential therapeutic use. We describe an isolation method, characterize a population, and investigate its potential for cell banking and thus suitability as a potential product for cell grafting therapies. Our results show hFDF and a bone marrow-derived mesenchymal stem cell (BM-MSC) line shared identification markers and in vitro multilineage differentiation potential into osteogenic, chondrogenic, and adipogenic lineages. The hFDF population exhibited similar cell characteristics as BM-MSC while producing lower pro-inflammatory cytokine IL-6 levels and higher levels of the wound healing factor hepatocyte growth factor. We demonstrate in vitro differentiation of hFDFs, which may be a problem in maintaining long-term lineage stability, potentially limiting their use for cell banking and therapy development.

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

Original Article:

Yoram Vodovotz, Richard L. Simmons, Derek Barclay, Jinling Yin, Bahiyyah S. Jefferson, **Ruben Zamora**. Decoding the secreted inflammatory response of primary human hepatocytes to hypoxic stress in vitro. Ann Transl Med 2019;7(16):371. doi: 10.21037/atm.2019.07.09.

ABSTRACT

Background: The cellular and molecular response of liver cells to hypoxic

stress is not fully understood. We used computational modeling to gain insights into the inflammatory response of primary human hepatocytes (HC) to hypoxic stress in vitro.

Methods: Primary HC from cancer patients were exposed to hypoxia (1% O2) or normoxia (21% O2) for 1–48 h, and the cell supernatants were assayed for 21 inflammatory mediators. Data were analyzed by Two-Way ANOVA, Dynamic Bayesian Network (DBN) inference, Dynamic Network Analysis (DyNA), and Time-interval Principal Component Analysis (TI-PCA).

Results: The chemokines MCP-1/CCL2 and IP-10/CXCL10, along with the cytokines interleukin (IL)-2 and IL-15 were altered significantly over time in hypoxic vs. normoxic HC. DBN inference suggested central, coordinating roles for MCP-1 and IL-8 in regulating a largely conserved inflammatory program in both hypoxic and normoxic HC. DyNA likewise suggested similar network trajectories of decreasing complexity over time in both hypoxic and normoxic HC, though with differential connectivity of MCP-1, IP-10, IL-8, and Eotaxin. TI-PCA pointed to IL-1β as a central characteristic of inflammation in hypoxic HC across all time intervals, along with IL-15 and IL-10, vs. Eotaxin, IL-7, IL-10, IL-15, and IL-17A in normoxic HC.

Conclusions: Thus, diverse human HC appear to respond in a largely conserved fashion to cell culture stress, with distinct characteristics based on the presence or absence of hypoxia.

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

Original Article:
Mooring M, Fowl BH, Lum SZC, Liu Y, Yao K, Softic S, Kirchner R, Bernstein A, **Singhi AD**, Jay DG, Kahn CR, Camargo FD, **Yimlamai D**. Hepatocyte Stress Increases Expression of YAP and TAZ in Hepatocytes to Promote Parenchymal Inflammation and Fibrosis. Hepatology. 2019 Sep 10. doi: 10.1002/hep.30928. [Epub ahead of print] PMID: 31505040

ABSTRACT
Activated hepatocytes are hypothesized to be a major source of signals that drive cirrhosis, but the biochemical pathways that convert hepatocytes into such a state are unclear. We examined the role of the Hippo pathway transcriptional coactivators, YAP/TAZ in hepatocytes to facilitate cell-cell

interactions that stimulate liver inflammation and fibrosis. Using a variety of genetic, metabolic and liver injury models in mice, we manipulated Hippo signaling in hepatocytes and examined its effects in non-parenchymal cells to promote liver inflammation and fibrosis. YAP expressing hepatocytes rapidly and potently activate the expression of proteins that promote fibrosis (COL1A1, TIMP1, PDGFc, TGFβ2) and inflammation (TNF, IL1β). They stimulate expansion of myofibroblasts and immune cells followed by aggressive liver fibrosis. In contrast, hepatocyte-specific YAP and YAP/TAZ knockouts exhibit limited myofibroblast expansion, less inflammation, and decreased fibrosis after carbon tetrachloride injury despite a similar degree of necrosis as controls. We identified CYR61 as a chemokine that is upregulated by hepatocytes during liver injury but is expressed at significantly lower levels in mice with hepatocyte-specific deletion of YAP or TAZ. Gain and loss of function experiments with CYR61 in vivo point to it being a key chemokine controlling liver fibrosis and inflammation in the context of YAP/TAZ. There is a direct correlation between levels of YAP/TAZ and CYR61 in liver tissues of high-grade NASH patients. CONCLUSION: Liver injury in mice and humans increases levels of YAP/TAZ/CYR61 in hepatocytes, thus attracting macrophages to the liver to promote inflammation and fibrosis.

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

Funding Opportunities

Research Awards: Afdhal / McHutchison LIFER Award

American Association for the Study of Liver Diseases (AASLD)

Limited Competition: AIDS Malignancy Consortium (AMC) (UM1 Clinical Trials Required)

(RFA-CA-19-056)

National Cancer Institute

AASLD Foundation Grants

AASLD Foundation (The American Association for the Study of Liver Diseases) has partnered with Trialect to reach out to biomedical scientists and physicians interested in liver diseases research to submit applications for clinical, translational, and basic research grants as the deadlines are fast approaching. Eligibility depends on the type of grant. These programs are in general restricted to the institutions in the United States, Canada, and

Mexico.

Fast-Track Drug Discovery, and Technology Development program: If you have a small molecule/biologic/device/ other medical technologies that you are developing at your institution or a start-up company, which could potentially be commercialized, we bring artificial intelligence, big pharma/device companies, venture capital groups/investors/other funding organizations, and your technology licensing office to take your technology to the next level.

Please feel free to fill the application (beta portal) at **Technology Development Program**

Our mailing address is:
Pittsburgh Liver Research Center
200 Lothrop St. | Pittsburgh, PA 15261