Important Notification: DDW 2017 Abstract # 2669088

Accepted (as of 14-Feb-2017)

View Invitations

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- **ATTENTION: If you are accepting your invitation, you may be required to answer additional questions. Additional questions will appear below. Complete these questions and hit the SAVE button.**

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Session Information

Invitation Message

Print Invitation Message

Dear Joseph George,

Congratulations! On behalf of the AGA Institute Council, I am pleased to inform you that your abstract, Inhibition of γ-glutamyl transpeptidase attenuates hepatic ischemia-reperfusion injury in rats (2669088), has been selected for poster presentation during Digestive Disease Week® at McCormick Place, Chicago, IL, May 6-9, 2017. Please notify any co-authors of this acceptance. Details of your session follow:

SESSION DETAILS
Session Type: Poster Session
Session Title: Basic Mechanisms of Injury and Repair
Session Date: May 7, 2017
Presentation Title: Inhibition of γ-glutamyl transpeptidase attenuates hepatic ischemia-reperfusion injury in rats
Presentation Time: Noon to 2 p.m.

IMPORTANT INFORMATION

- You are required to respond to this invitation by Wednesday, Feb. 22, by 5 p.m. ET.

- Declining will result in an automatic withdrawal of your abstract.
- All poster sessions will take place in the MCP South Hall, open from 9:30 a.m. to 4 p.m.
- You must be present at your poster from noon - 2 p.m. on the day of your scheduled presentation.
- The maximum size of DDW poster presentations is 4 feet high by 8 feet wide.
- Any posters or poster tubes remaining in the Poster Hall after 6 p.m. will be discarded. Overnight storage is not permitted.

RESPOND
Indicate your response by clicking on either the "Accept Invitation" or "Decline Invitation" button at the bottom of this page.

REGISTER
All poster presenters are required to register for DDW and are responsible for all travel expenses. Important dates:

- Early bird registration closes March 22, 2017. Save money by registering early!
- On-site registration will be available.
- Registration rates can be found at the DDW website.

Register now.

PRESENTER GUIDELINES
For more information about presenting your poster and to download the full presenter guidelines, please visit the DDW website.

PRESENTER RESOURCES - Increase the visibility and reach of your science.

ePosters: Take your poster online, where attendees can access it during and after the meeting. We encourage you to submit an electronic version of your poster in addition to the paper format. You can include video clips and audio narration with your ePoster to further explain your data. A link to the ePoster submission site will be sent to you by email in late March. Visit the DDW ePosters archive to view examples from last year's meeting.

Poster Printing: DDW is offering a poster printing service for accepted poster presenters at DDW 2017. This professional poster service includes printing, packaging, and shipping directly to McCormick Place. The inclusive printing and delivery cost is $110 to $170, depending on selected size if ordered by the advance printing deadline. Poster presenters will receive an email with instructions in late March.

Poster Training Sessions: Learn techniques for effective poster presentations on May 6, 7 and 8 from 7:30-7:45 a.m. in the Poster Hall.

Video Promos: DDW invites you to submit a promotional video explaining the top reasons to attend your presentation for a chance to win free registration to DDW 2018. Upon approval, videos will be posted to the DDW YouTube Channel and may also be shared at other DDW social media sites. New for this year's meeting, presenting authors who submit a video will be entered in a drawing to win free registration to DDW 2018. The winner will be announced onsite in Chicago.

Videos should be at least 30 seconds but may not exceed three minutes in length. Please be sure to mention the title of your presentation along with the date and presentation number. Do not include any unpublished data in your video. Examples of last year's videos are available at the DDW YouTube Channel.

Videos will be accepted through April 21, 2017. Click here to submit your video.

Once again, congratulations on your accomplishment. We look forward to seeing you in Chicago.

Sincerely,

Maria T. Abreu, MD, AGAF
Chair, AGA Institute Council

Su1806

HEDGEHOG-DEPENDENT YAP SIGNALING ACTIVATES SERINE BIOGENESIS AND GLUTAMINOLYSIS TO PROMOTE HEPATIC STELLATE CELL TRANSDIFFERENTIATION

George Dalton, Gregory A. Michelotti, Yuping Chen, Guanhua Xie, Marzena Swiderska-Syn, Anna Mae Diehl

Background: Liver fibrosis involves accumulation of myofibroblasts (MF) derived from quiescent hepatic stellate cells (Q-HSCs). Hedgehog (Hh) signaling regulates this HSC transdifferentiation by inducing a metabolic shift towards aerobic glycolysis. During this metabolic switch, MF-HSCs undergo changes in glycolytic gene expression to help meet the energetic needs to sustain a hyperproliferative state. However, increased aerobic glycolysis alone cannot meet the metabolic demands of proliferating MF-HSCs. The tricarboxylic acid (TCA) cycle is also a source of energy production whose continued functioning requires replenishment of carbon intermediates which can occur via glutaminolysis. Serine (Ser) biogenesis also contributes to energy homeostasis by regulating levels of α-ketoglutarate, a key TCA cycle intermediate. We hypothesized that Ser biogenesis and glutaminolysis help meet the metabolic demands of pro-proliferative HSCs and show this occurs in a Hh-YAP-dependent manner. **Methods**: *In vitro*: Differentially expressed genes for Ser biogenesis and glutaminolysis were identified by microarray analysis of mouse Q-HSCs and MF-HSCs and validated by qRT-PCR, western blot (WB), immunocytochemistry (ICC), and quantitative metabolomics (QM). To assess glutaminolysis, glutamine (Gln) supplementation was performed in HSCs and proliferation, migration, and invasion were quantified. Hh signaling was investigated via GLI overexpression and by Cre-mediated Smoothened (Smo) deletion in HSCs isolated from Smo-LoxP mice. YAP signaling was investigated via lentiviral shRNA knockdown of YAP expression in HSCs. *In vivo*: Ser biogenesis and glutaminolysis were examined by qRT-PCR, WB, and immunohistochemistry in three models of liver fibrosis in mice involving CCl_4 injection, bile duct ligation, and methionine choline deficient diet. **Results**: *In vitro*: Genes encoding enzymes for Ser biogenesis and glutaminolysis were induced in MF-HSCs (PHGDH 26.8 ± 6.2; PSAT 21.0 ± 3.8; PSPH 6.8; SHMT 2.0 ± 0.1; GLS 2.9 ± 0.3; SNAT1 7.0; SNAT2 2.7). WB and ICC confirmed increased protein expression in MF-HSCs. QM showed increased glycine/Ser levels in MF-HSCs. GLI overexpression increased expression of these genes, while disrupting the Hh signaling intermediate Smo decreased gene expression in MF-HSCs. Silencing YAP expression inhibited gene expression of GLI and these metabolic enzymes in MF-HSCs. Gln depletion reduced proliferation, migration and invasion in cultured HSCs. *In vivo*: Enzymes for Ser biogenesis and glutaminolysis were increased in mouse models of liver injury/fibrosis. Inhibiting Hh signaling in αSMA(+) cells repressed whole liver PHGDH expression and fibrosis. **Conclusion**: These studies elucidate the connection of Hh-dependent YAP activation to Ser biogenesis and glutaminolysis and show this is a hallmark of metabolic reprogramming occurring in MF-HSCs.

Su1807

MMP-9 MODULATION OF INTESTINAL EPITHELIAL TIGHT JUNCTION BARRIER IN-VITRO AND IN-VIVO IS MEDIATED BY MYOSIN LIGHT CHAIN KIANSE (MLCK)

Rana Al-Sadi, Manmeet Rawat, Thomas Y. Ma

Background: Matrix Metalloproteinases 9 (MMP-9) has been implicated to have a key pathogenic factor in inflammatory bowel disease. MMP-9 is markedly elevated in intestinal tissue of patients with inflammatory bowel disease (IBD). IBD patients have a defective intestinal tight junction (TJ) barrier manifested by an increase in intestinal permeability. Though loss of epithelial barrier function is a key factor for the development of intestinal inflammation, the role of MMP-9 in intestinal barrier function remains unclear. **Aims:** The purpose of this study was to investigate the effect of MMP-9 on intestinal epithelial TJ barrier and to delineate the intracellular mechanisms involved using *in-vitro* (filter-grown Caco-2 monolayers) and in-vivo (small intestine perfusion) systems. **Results:** 1) MMP-9 caused a time- and dose-dependent drop in Caco-2 transepithelial resistance (TER) and increase in Caco-2 inulin flux. 2) MMP-9 induced increase in Caco-2 TJ permeability was associated with an increase in myosin light chain kinase (MLCK) mRNA and protein expression 3) Inhibition of MLCK with pharmacologic inhibitor ML-7 (10 μM) and by siRNA induced MLCK silencing prevented the MMP-9 induced drop in Caco-2 TER and increase in inulin flux. 4) MMP-9 caused an increase in mouse intestinal TJ permeability *in-vivo*, which was correlated with an increase in MLCK mRNA and protein expression. 5) *In-vivo* siRNA induced knock-down of mouse intestinal MLCK prevented the MMP-9 induced increase in mouse intestinal TJ permeability. **Conclusion:** In conclusion, our studies show that MMP-9 causes an increase in intestinal epithelial TJ permeability *in-vitro* and *in-vivo* that was mediated by an increase in MLCK expression. And, inhibition of MLCK attenuates MMP-9-induced epithelial permeability. These findings suggest an important role of MMP-9 in modulation of intestinal epithelial permeability via MLCK.

Su1808

NGF ACCELERATES GASTRIC ULCER HEALING IN AGING RATS BY INCREASING ANGIOGENESIS AND IMPROVING EPITHELIAL REGENERATION: NEW INSIGHT INTO ULCER HEALING USING REAL-TIME CONFOCAL LASER ENDOMICROSCOPY

Andrzej S. Tarnawski, Amrita Ahluwalia, Michael K. Jones, Tomasz Brzozowski

Background: Nerve growth factor (NGF) is critical for growth, survival and regeneration of neurons. NGF expression in gastric mucosa beyond neural compartments, and its possible role in gastric ulcer (GU) healing are not known. Our aims were to determine if local treatment of GUs in aging rats with NGF can improve GU healing, to identify targets of NGF actions, and to determine whether confocal laser endomicroscopy (CLE) can detect abnormal mucosal regeneration during GU healing. **Methods:** GUs were induced in aging rats (24 mo old) by local application of acetic acid. Thirty min and 72 hr after GU induction either PBS (control) or NGF (100 μg/kg bw) was injected into the submucosa at the site of GU induction. In a separate group, FITC-labeled NGF was injected into the submucosa at the site of GU induction. **Studies** 3 weeks after GU induction: 1) Mucosal blood flow by a laser Doppler flowmeter; 2) GU size; 3) Quantitative histologic assessment: regeneration of epithelial and vascular structures; size and number of blood vessels; 4) Incorporation of FITC-labeled NGF into gastric tissues; 5) Expression of NGF, its TrkA receptor & VEGF by immunostaining; 6) *In vivo* visualization of mucosal structures in normal and ulcerated gastric mucosa using CellVizio CLE system with needle based probe and i.v. fluorescein. **Results:** In the PBS-treated control group, GUs were present in all rats at 3 weeks after ulcer induction and regenerating glands were dilated and distorted compared with normal gastric mucosa. CLE imaging demonstrated in scars/margins of GU, distorted and enlarged (up to 5x normal) blood vessels with turbulent RBC flow and increased vascular permeability representing abnormal angiogenesis. NGF treatment significantly accelerated GU healing at 3 weeks vs. the PBS treated control group as reflected by >5-fold reduced GU size ($P<0.01$), increased mucosal blood flow in GU scars/margins by 37% and increased microvessel density in granulation tissue by 62% (both $P<0.01$) reflecting increased angiogenesis. The regeneration of blood vessels and epithelial components in GU scars was significantly increased in the NGF treated group. Following local NGF treatment of GUs in aging rats, NGF expression increased in epithelial cells and in endothelial cells (ECs) of blood vessels in sub-mucosa and GU granulation tissue vs. PBS treated control rats. Locally injected FITC-labelled NGF was retained in ECs of blood vessels in gastric granulation tissue and mucosa of aging rats at 3 weeks after GU induction. **Conclusions:** 1) Local NGF treatment accelerates GU healing in aging rats and improves quality of mucosal regeneration. 2) Locally administered NGF is incorporated into regenerating blood vessels and stimulates angiogenesis. 3) CLE provides new, real time insight into GU healing. 4) This study uncovered a novel role of NGF in GU ulcer healing beyond neural regeneration.

Su1809

INHIBITION OF Î"-GLUTAMYL TRANSPEPTIDASE ATTENUATES HEPATIC ISCHEMIA-REPERFUSION INJURY IN RATS

Joseph George, Nobuhiko Hayashi, Mutsumi Tsuchishima, Mikihiro Tsutsumi

Background and Aims: Ischemia-reperfusion (IR) injury is a major clinical problem and is associated with numerous adverse effects. GGsTop [2-amino-4{[3-(carboxymethyl)phenyl](methyl)phosphono}butanoic acid] is a highly specific and irreversible g-glutamyl transpeptidase (g-GT) inhibitor. We studied the protective effects of GGsTop on IR induced hepatic injury in rats. ***Methods:*** Ischemia was induced by clamping the portal vein and hepatic artery of left lateral and median lobes of the liver. Before clamping, saline (IR group) or saline containing 1 mg/kg body weight of GGsTop (IR-GGsTop group) was injected into the liver through inferior vena cava. At 90 min of ischemia, blood flow was restored. Blood was collected before induction of ischemia and prior to restoration of blood flow, and at 12, 24, and 48 h after reperfusion. All the animals were sacrificed at 48 h after reperfusion and the livers were harvested. ***Results:*** Serum levels of ALT, AST, and g-GT were significantly lower after reperfusion in IR-GGsTop group compared to IR group. Massive hepatic necrosis was present in IR group, while only few necroses were present in IR-GGsTop group. Treatment with GGsTop increased hepatic GSH content, which was significantly reduced in IR group. Furthermore, GGsTop prevented increase of hepatic g-GT, malondialdehyde, 4-hydroxynonenal, and TNF-α while all these molecules significantly increased in the IR group. ***Conclusions:*** Treatment with GGsTop increased glutathione levels and prevented formation of free radicals in the hepatic tissue that lead to decreased IR-induced liver injury. GGsTop could use as a pharmacological agent to prevent IR-induced liver injury and the related adverse events.

Su1810

Δ^9-TETRAHYDROCANNABINOL INHIBITS TRANSFORMING GROWTH FACTOR Î'1 INDUCED PRO-FIBROTIC AND NOCICEPTIVE GENE EXPRESSION AND STIMULATES INTERLEUKIN 1Î' MRNA EXPRESSION IN HUMAN INTESTINAL MYOFIBROBLASTS

Christopher Broxson, Ellen M. Zimmermann

Marijuana improves pain and other GI symptoms in patients with inflammatory bowel disease (IBD). In other systems its effect is primarily anti-inflammatory, however, its role in fibrosis is less clear with evidence for both anti- and pro-fibrotic effects dependent upon specific cannabinoid interaction with CB1 or CB2 receptors. Many studies rely on synthetic cannabinoids, which do not accurately mimic phytocannabinoids. We used Δ^9-Tetrahydrocannabinol (THC), the DEA schedule 1 compound that is the most abundant psychoactive cannabinoid in cannabis, to study its role in intestinal fibrosis using primary human intestinal myofibroblasts (hIMF) stimulated with TGFβ1 (TGF). **Methods:** For cytotoxicity studies, hIMFs were grown in standard culture conditions and treated with THC (20nM to 30μM). Cell growth was recorded for 48 hours to establish a range of THC dosing. Human IMFs were treated with THC (1μM, 0.5μM, 0.25μM) or vehicle 24 hours before exposure to [5ng/ml] of TGF (or vehicle) for an additional 24 hours. Cellular mRNA was isolated to analyze fibrotic, inflammatory, nociceptive, and cannabinoid receptor gene expression using quantitative real-time PCR. **Results:** Human IMFs were more sensitive to THC than most cell types and displayed morphological changes suggestive of apoptosis at concentrations above 1.5μM. The TGFb1-induced increase in procollagen I (*COL1A2*) and III (*COL3A1*), and the profibrotic factor *CTGF* were decreased by THC, particularly at the higher doses (Fig.1-3). The TGFb1-induced increase in *TIMP1* mRNA, the matrix metalloproteinase inhibitor, was also decreased by THC (Fig. 4). *PPARg* mRNA, shown in hepatic stellate cells to mediate anti-fibrotic effects, was increased over vehicle at 1μM THC (Fig. 5). These findings demonstrate a consistent anti-fibrotic effect of THC in this model. THC inhibited the TGFb1-induced increase in *IL-6* mRNA. THC strikingly increased IL-1b mRNA; TGFb1 did not increase *IL-1* mRNA, and TGFb1 and THC together did not increase *IL-1* mRNA. The transient receptor potential vanilloid 1 (*TRPV1*) mRNA, involved in nociception and crosstalk with the cannabinoid receptors, were decreased at all doses of THC (Fig. 6). In our cells, canonical receptor mRNAs (CB1 and CB2) were very sparse and only amplified in a few samples at very high cycle numbers. **Conclusion:** Our findings demonstrate a consistent anti-fibrotic effect of THC in this model. THC effectively blocked the TGF-induced increase in profibrotic factors.