1920 Trpv4 Modulates Cyp2e1-Mediated Oxidative Stress Toxicity and Kupffer Cell Activation in Nonalcoholic Steatohepatitis

R. K. Seth[2], S. Das[2], D. Dattaroy[2], F. Alhasson[2], G. A. Michelotti[1], M. Nagarkatti[6], P. Nagarkatti[6], P. D. Bell[4], W. B. Liedtke[3], A. M. Diehl[3] and S. Chatterjee[2]. *[1]Metabolon, Inc., Durham, NC; [2]ENHS, University of South Carolina, Columbia, SC; [3]Gastroenterology, Duke University, Durham, NC; [4]Medicine, University of Alabama, Birmingham, AL; [5]Neurology, Duke University, Durham, NC and [6]PMI, University of South Carolina SOM, Columbia, SC.*

Emerging evidence shows that oxidative stress via the activation of cytochrome p450 2E1 (CYP2E1) is key to progression of inflammation in nonalcoholic steatohepatitis (NASH). We have shown previously that CYP2E1 mediated oxidative stress and macrophage polarization in NASH was attenuated by NO donor. However the molecular mediators and its pathways that regulate CYP2E1 mediated oxidative stress in NASH remains obscure. For this study we used a high fat diet induced obese mice as *in vivo* and HepaRG, Kupffer cells as *in vitro* model. The CYP2E1 substrate pyrazole or BDCM were used to induce CYP2E1 mediated oxidative stress, inflammation and NASH pathology. Results showed that the transient receptor potential vanilloid channel 4 (TRPV4) expression and protein levels were significantly elevated in parallel to increases in CYP2E1 and correlated well with increased lipid peroxidation, IL1β, MCP1, TNFα and HMGB1 levels in the NASH livers and in Kupffer cells. TRPV4 knockout (KO) mice showed increased CYP2E1 protein, lipid peroxidation, inflammatory cytokines, infiltration of leukocytes, sinusoidal endothelial dysfunction (SED) maker genes (CD34, cdh5, ICAM-1 and VEGFR2), HMGB1 levels, decreased phosphorylated endothelial nitric oxide synthase (NOS3) and exhibited early morbidity as compared to wildtype mice with NASH. Mechanistically, diallyl sulfide (CYP2E1 inhibitor) or NO donor DETANONOate administration to TRPV4 KO mice completely abrogated enhanced NASH symptoms and morbidity. Interestingly, use of NO donor significantly decreased CYP2E1-mediated lipid peroxidation, an indirect measure of its activity, proinflammatory genes and SED marker in TRPV4 KO mice. The results obtained show that TRPV4, a crucial protein responsible for sensing changes in osmotic pressure and Ca2+ also regulates CYP2E1-mediated oxidative stress, inflammation and endothelial injury probably by activating NOS3 and release of nitric oxide. Based on the above, targeting TRPV4 or its downstream signaling cascade might be a promising therapeutic strategy in NASH.

1921 Comparison of Early vs Late Pulmonary Toxicity in Crystalline Silica Exposed Rats

P. Joseph, J. Roberts, T.-h. Chen, W. McKinney, M. Orandle and C. Umbright. *NIOSH, Morgantown, WV.*

Occupational exposure to respirable crystalline silica can result in silicosis in addition to other adverse health effects. Currently, we investigated and compared the early vs. late pulmonary toxicity induced by inhalation exposure of rats to crystalline silica. In addition, differential expression of specific genes involved in known mechanisms of silicosis viz. inflammation and fibrosis, were determined in the principal target organ of silica toxicity (lung) and a surrogate tissue (blood) in the rats. Rats were exposed by inhalation to air (control) or respirable crystalline silica (Min-U-Sil 5 Silica) at a concentration of 15 mg/m3, for 6 hours per day for 5 days. The rats, following exposure, were maintained under standard animal housing conditions either for 1- or 9-months and euthanized. Silica-induced pulmonary toxicity was determined on the basis of lung histology, and bronchoalveolar lavage (BAL) parameters of toxicity (lactate dehydrogenase activity, number of alveolar macrophages and polymorphonuclear leukocytes, and generation of reactive oxygen species). Differential expressions of specific genes involved in inflammation and fibrosis were determined in the lungs and blood using PCR arrays. Mild inflammation was the only histological change detected in the rat lungs at the 1-month post-exposure period whereas type II pneumocyte hyperplasia and fibrosis were detected in the lungs at the 9-months post-exposure period. Similarly, compared to the early time period, more significant changes in all BAL parameters of toxicity were noticed in the rats at the late post-exposure period. Differential expression of several genes associated with inflammatory response and fibrosis were detected in the lungs and blood of all of the silica exposed rats. However, both the number of significantly differentially expressed genes and the changes in gene expression were greater at the 9-month post-exposure period compared with the 1-month period. Collectively, these results, demonstrated the critical role of post-exposure time interval in the progression of silica-induced pulmonary toxicity in rats.

1922 Understanding Spatiotemporal Signaling Associated with Inflammation Caused by a Physical Stressor

J. Boyd[1], A. Han[1], E. Fabyanic[1], M. Prediger[1] and H. Currie[2]. *[1]Bennett Department of Chemistry, West Virginia University, Morgantown, WV and [2]Department of Chemistry and Physics, California University of Pennsylvania, California, PA.*

While temporal aspects of inflammation have been extensively studied and provide an important understanding of the processes involved in both toxicity and repair, research into the disparate spatial response to localized inflammation is sparse. This study addresses spatial and temporal differences of phosphoproteins found in muscle tissue following a traumatic femur fracture in Sprague-Dawley rats, which are further compared to co-localized cytokine responses. In particular, several proteins (AKT, ERK, c-Jun, CREB, JNK, MEK1, and p38) associated with inflammation, new tissue formation, and remodeling were found to exhibit significant spatial and temporal differences in response to localized traumatic injury. In addition, post-translational phosphorylation levels were measured to further capture the contribution of protein activity during the recovery phase. Our results identified generally lower degrees of phosphorylation at the site of injury (compared to sites located further away) at early time points (beginning immediately following fracture through 24 hours). Further, an increase of phosphorylation for select proteins (at or near the injury site) was observed at the last time point measured in this study (168 hours). Finally, phosphoprotein measurements were found to be significantly correlated to cytokine responses (IL-1α, IL-1ß, IL2, IL6, TNF-α, and MIP-1α), suggesting the importance of coordinated intracellular and extracellular activity during crucial periods of inflammation and repair. This study represents a first attempt to monitor coordinated changes in extracellular and intracellular signaling related to traumatic injury in muscle tissues, which may provide a framework for future research to improve our understanding of the spatiotemporal response inflammation.

1923 Suppresion of Gastric Inflammatatory Markers and Mitochondrial Apoptotic Pathway by Methanol Extract of *Chasmanthera dependens* Stem in Ethanol-Induced Gastric Ulcer Healing

A. S. Tijani, O. E. Farombi and S. B. Olaleye. *Drug Metabolism and Toxicology Research Laboratories, Department of Biochemistry, University of Ibadan, Ibadan, Nigeria; Gastrointestinal Research Unit, Department of Physiology, University of Ibadan, Ibadan, Nigeria.*

Neutrophil infiltrations and continuous generation of reactive oxygen species have been reported to delay gastric ulcer healing in ethanol-induced gastric ulcer. This study investigated the potential of the methanol extract of *Chasmanthera dependens* (MECD) stem in healing ethanol-induced gastric ulcer in male Wistar rats. Thirty six rats were divided into six groups of six rats each and treated orally. Group 1 rats served as control group and received 1 ml/kg body weight of 1% gum acacia solution; groups 2-6 rats were given acidified ethanol to induce gastric ulcer. Groups 3, 4 and 5 rats were treated with 200, 400 and 800 mg/kg body weight of MECD stem while group 6 rats were treated with 50 mg/kg body weight of cimetidine (CIM) for fourteen days after ulcer induction. Ulcer score, ulcer index and levels of tumor necrosis-alpha (TNF-α), interleukin-1beta (IL-1β), cytochrome c (Cyt-c), caspase-9 (Casp-9) and caspase-3 (Casp-3) were assessed in the serum and gastric tissues were used for histological examination and terminal deoxynucleotidyl transferase-mediated nick end-labeling (TUNEL) assay. Acidified ethanol caused severe gastric mucosa damage with ulcer score and ulcer index of 19.00 ± 1.00 and 2.86 ± 0.37 at $p<0.01$ respectively. But treatments with MECD significantly heal the ulcer with percentage ulcer healing of 78.36 ± 0.62, 92.36 ± 1.86, 81.41 ± 0.25 for different doses of MECD and CIM, 72.12 ± 0.30 respectively. Similarly, ethanol administration increased TNF-α, IL-1β, Cyt-c, Casp-9, Casp-3 levels and number of positive apoptotic nuclei in ulcerated untreated group, while MECD or CIM treatment for 14-days significantly reversed these observations and the histological examination revealed restitution of the gastric tissues. The results show that administration of MECD stem promotes gastric ulcer healing by suppressing the inflammatory markers and inhibiting the intrinsic apoptotic pathway and as such could be relevant in pathologies involving gastrointestinal dysfunction such as ulcer.

The Toxicologist

Supplement to *Toxicological Sciences*

55th Annual Meeting and ToxExpo™

SOT

New Orleans, Louisiana

March 13–17, 2016

OXFORD
UNIVERSITY PRESS

ISSN 1096-6080
Volume 150, Issue 1
March 2016

www.toxsci.oxfordjournals.org

The Official Journal of the Society of Toxicology

SOT | Society of Toxicology

Creating a Safer and Healthier World by Advancing the Science and Increasing the Impact of Toxicology

www.toxicology.org

Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 55th Annual Meeting of the Society of Toxicology, held at the New Orleans Ernest N. Morial Convention Center, March 13–17, 2016.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 603.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 629.

The abstracts are reproduced as accepted by the Scientific Program Committee of the Society of Toxicology and appear in numerical sequence. Author names which are underlined in the author block indicate the author is a member of the Society of Toxicology. For example, J. Smith.

Scientific Session Types:

- CE Continuing Education Courses
- EC Education-Career Development Sessions
- FS Featured Sessions
- HH Historical Highlights Sessions
- IS Informational Sessions
- PL Platform Sessions
- PS Poster Sessions
- RI Regional Interest Sessions
- R Roundtable Sessions
- S Symposium Sessions
- W Workshop Sessions

The 2016 SOT Mobile Event App and Online Planner

The Mobile Event App and Online Planner are available via the SOT website and app marketplaces. These mobile tools enable you, the attendee, to engage with organizers, exhibitors, and each other, and to manage your time and maximize your experience during the Annual Meeting. You also can access some ePosters electronically via the Mobile Event App until May 11, 2016.

To cite a 2016 SOT Annual Meeting Abstract, please format as follows: *The Toxicologist*, Supplement to *Toxicological Sciences*, 150 (1), Abstract #__, 2016, Title, First Author.

Copies of *The Toxicologist* are available at $40 each plus shipping ($15 shipping & handling in the USA and $50 for overseas shipments) from:

Society of Toxicology
1821 Michael Faraday Drive, Suite 300 • Reston, VA 20190

www.toxicology.org