specificities. Tissue distribution of ALDH7A1 protein in mice reveals highest expression in liver, kidney and brain, followed by pancreas and testes. ALDH7A1 protein is found in the cytosol, nucleus and mitochondria, thus making it unique among the ALDH enzymes. Analysis of human and mouse cDNA sequences revealed mitochondrial and cytosolic transcripts that are differentially expressed in a tissue-specific manner in mice. In conclusion, ALDH7A1 is a novel ALDH expressed in multiple subcellular compartments that protects against hyperosmotic stress by generating osmolytes and metabolizing toxic aldehydes.

PL 596 AHR-DEPENDENT LIPID MEMBRANE REMODELING: AN EARLY STEP FACILITATING BENZO[A]PYRENE-INDUCED APOPTOSIS.

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Benzo[a]pyrene (B[a]P) often serves as a model to study the mutagenic and carcinogenic polycyclic aromatic hydrocarbons (PAHs). Our previous works have suggested primordial role of the plasma membrane, more specifically the membrane fluidity, in B[a]P-induced apoptosis (Gorria et al., Ann NY Acad Sci, 2006). The plasma membrane has various microstructures that are important for its function, including the presence of cholesterol-rich-microdomains (CRM). By analysing CRM from rat liver F258 epithelial cells using immunofluoresence, lipid analysis, RT-PCR and western blotting, we found that B[a]P induced re-organization of membrane CRM via cholesterol depletion, fatty acid composition changes, and ganglioside GM1 redistribution. Studies with siRNA showed that the depletion of cholesterol was caused by down-regulation of 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase, HMGCR), as a result of B[a]P-induced aryl hydrocarbon receptor (AhR) binding and H2O2 formation. Addition of mevalonate, the product of HMG-CoA reductase, inhibited B[a]P's early effects on the plasma membrane facilitating the triggering of apoptosis. In contrast, no effects on the classical initiation steps B[a]P-induced p53 phosphorylation and H2O2 production were seen. Intracellular pH measurements suggest that the remodelling plays a critical role in B[a]P-induced alkalinization observed during the early phase of apoptosis. Our data provide evidence that B[a]P via AhR binding and H2O2 formation change the plasma membrane microstructure, thereby enhancing apoptosis.

PL 597 OXIDATIVE LIPIDOMICS OF GAMMA-RADIATION INDUCED LUNG INJURY.

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Oxidative damage has been suggested to play a significant role in pathogenesis of gamma-irradiation-induced lung injury. Endothelium is likely a preferred target for early irradiation induced damage and apoptosis. Oxidized phospholipids (PLs) participate in apoptotic signaling. Therefore, we performed oxidative lipidomics analysis of PLs in cells and animals after irradiation. C57BL/6NHsd female mice were subjected to total body irradiation (TBI) at doses of 5, 10 and 15Gy and sacrificed 4h and 24h thereafter. We found that irradiation caused apoptosis as early as 4h after TBI, as revealed by caspase-3/7 activation. We demonstrated that the pattern of PL oxidation 4 and 24 h after TBI is non-random and does not follow the PL abundance in the lung. We established that two anionic PLs – mitochondria-specific cardiolipin (CL) and plasma membrane phosphatidylserine (PS) – are the two major oxidized PLs in the lung while more abundant PLs such as PC and PE – remain non-oxidized. ESI-MS and LC-MS analysis revealed the formation of several CL and PS oxygenated molecular species in irradiated lung. Hydrolysis of CL and PS by phospholipase A2 and subsequent analysis of fatty acids by LC/ESI-MS revealed the presence of di-hydroxy and mono-hydroperoxy molecular species of linoleic acid. The same two anionic PLs – CL and PS – were oxidized in mouse pulmonary endothelial cells (MLECs) after exposure to dose of irradiation (15Gy). This oxidation of MLEC PLs was accompanied by significant activation of caspases 3/7 and phosphorylation of scramblase 3, an enzyme responsible for trans-membrane migration of CL in mitochondria during apoptosis. We speculate that cyt c driven oxidation of CL and PS is associated with the execution of apoptosis in pulmonary endothelial cells thus contributing to endothelial cell dysfunction in gamma-irradiation lung injury. Supported by NIH NIAID U19 AI068021, HL70755, HL094488.

PL 598 OXIDATIVE LIPIDOMICS OF HYPEROXIA-INDUCED ACUTE LUNG INJURY.

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Reactive oxygen species have been considered to play a significant role in hyperoxia-induced acute lung injury (HALI), in part, by inducing apoptosis of pulmonary endothelium involving both extrinsic and intrinsic pathways. However, signaling roles of phospholipid (PL) oxidation products in endothelial apoptosis in the lung have not been studied. We employed oxidative lipidomics approach to identify individual molecular species of PLs involved in apoptosis-associated peroxidation process in hyperoxic lung. C57BL mice were sacrificed 72h after exposure to hyperoxia (99% oxygen). We found that HALI induced apoptosis (as evidenced by caspase 3/7activation) accompanied by non-random oxidation of pulmonary lipids. Two anionic PLs – mitochondria-specific cardiolipin (CL) and plasma membrane phosphatidylserine (PS) – were the two major oxidized PLs in hyperoxic lung. ESI-MS analysis revealed the formation of several oxygenation products in CL and PS. Quantitative LC-MS analysis revealed significant decrease of CL and PS molecular species containing C18:2, C20:4, C22:6 and C22:5 fatty acids. When lung PLs were incubated with cyt c/H2O2 comparable pattern of PL oxidation was observed. Similar to HALI, exposure of mouse pulmonary endothelial cells (MLEC) to hyperoxia (95% oxygen) resulted in activation of caspase 3/7. Moreover, oxygenated molecular species were found in the same two anionic PLs – CL and PS - in MLEC exposed to hyperoxia. Furthermore, we documented significantly decreased content of CL molecular species containing C18:2 and C20:4 as well as PS molecular species containing C22:6, C22:5 and C22:4. Treatment of MLEC with mitochondria targeted radical scavenger GS-nitroxide, XJB-131, resulted in significantly lower oxidation of both CL and PS. We speculate that cyt c driven oxidation of CL and PS is associated with the execution of apoptosis in pulmonary endothelial cells thus contributing to HALI. Supported by NIH HL70755, HL094488.

PL 599 PHOSPHOLIPID (PL) OXIDATIVE METABOLISM DURING MACROPHAGE RESPONSE TO ENVIRONMENTAL AGENTS.

V. A. Tyurin[1, 2], D. Winnica[1], F. Fazzi[1], W. Feng[1, 2], Y. Tyurina[1, 2], N. Stewart[3], E. Kisin[4], A. Murray[4], A. Shvedova[4], B. Pitt[1], V. Kagan[1, 2] and L. Ortiz[1]. *[1]EOH, University of Pittsburgh, Pittsburgh, PA, [2]CFRAH, University of Pittsburgh, Pittsburgh, PA, [3]Medicine, University of Pittsburgh, Pittsburgh, PA and [4]Physiology/Pathology Research Branch, Health Effects Laboratory Division, NIOSH, Morgantown, WV.*

Macrophages play a fundamental role during the clearance of environmental agents from the lung. During this process macrophages are activated to release inflammatory mediators and undergo apoptosis. PLs and their metabolites are involved in inflammation and cell death. However, no comprehensive studies, using contemporary research tools such as mass spectrometry (MS), addressing the oxidation or hydrolysis of PLs (phosphatidylcholine, PC, phosphatidylethanolamine, PE, phosphatidylserine, PS, phosphatidylinositol, PI, and cardiolipin, CL) in macrophages are available at this time. Therefore, we conducted a quantitative characterization, using ESI-MS and fluorescence HPLC/Amplex Red assays, of the oxidative and phospholipase A hydrolysis of individual molecular species of major classes of PLs on silica, zymozan, or single wall carbon nanotube (SWCNT) exposed macrophages (Raw 264.7, IC-21, or primary from C57BL/6 mice). We report that following exposure to silica, SWCNT, or zymozan macrophages experience a rapid, and selective peroxidation of anionic PLs in a manner that is independent of their cell abundance (CL>>PS>>PI). Oxidation of CL in response to silica is followed by the accumulation of the hydrolyzed moiety of CL, monolyso-CL, and oxidized free fatty acids shortly after the release of cyt C, and the externalization of PS in the cell membrane. Subsequently, oxidation of the same species of anionic PLs was identified in lungs of C57BL/6 mice exposed to SWCNT. We concluded that anionic PLs- are important mediators of the macrophage response to environmental agents and that they undergo a highly regulated metabolism during macrophage apoptosis. Supported by NIOSH OH008282, NORA 927000Y, NIH HL70755, HL094488.

PL 600 VALIDATION OF A NON-HUMAN PRIMATE TELEMETRY MODEL FOR ASSESSMENT OF CONTRACTILITY PARAMETERS.

A. Simonnard, G. Froget, A. Bétat and R. Forster. *CIT, Evreux, France.*

Following the implementation of ICH S7b Guidelines, the evaluation of cardiac safety of new chemical entities routinely includes potential adverse effect on hemodynamic, chronotropic and dromotropic effects. However, potential inotropic ef-

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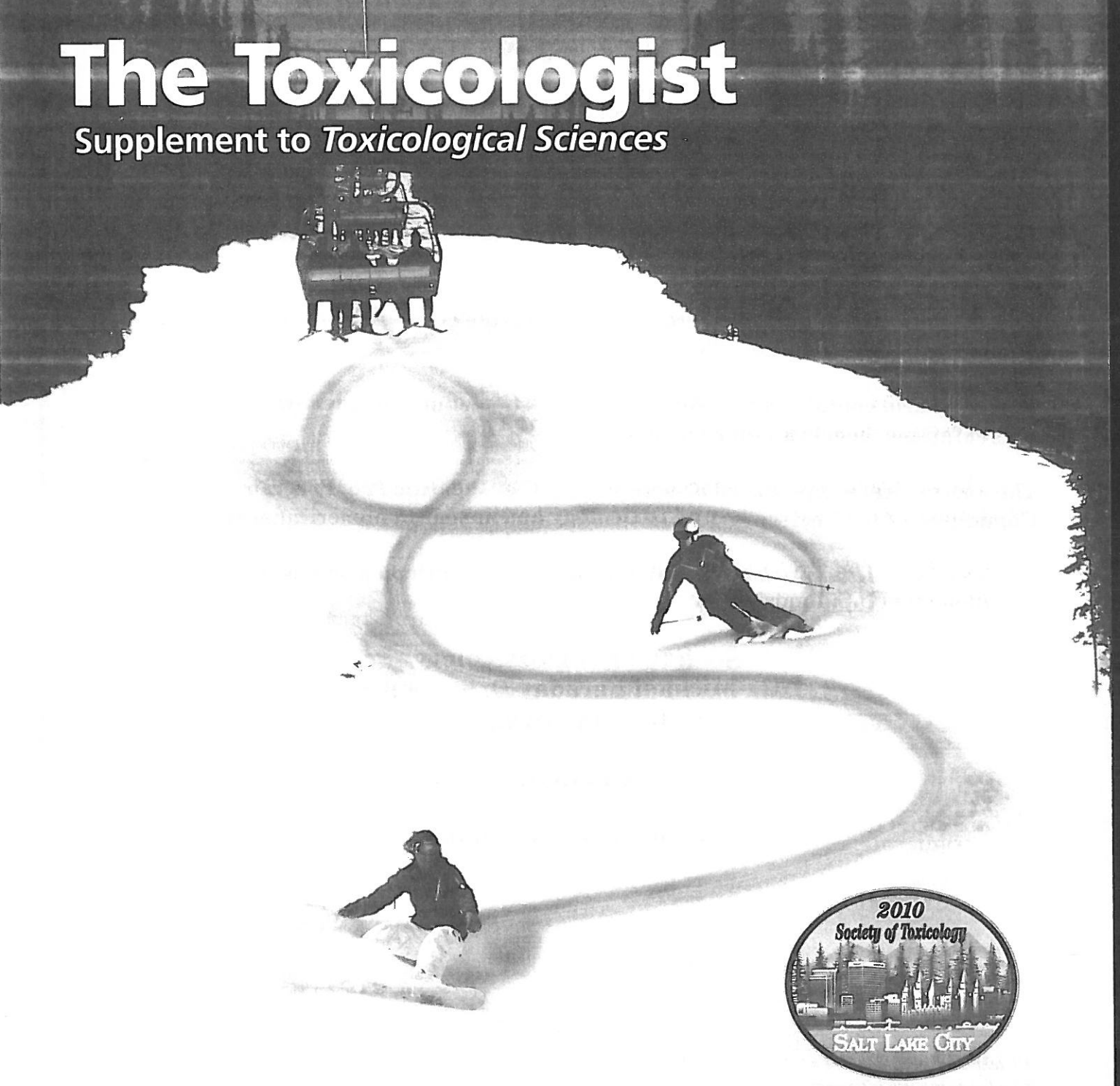

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 49th Annual Meeting of the Society of Toxicology, held at the Salt Palace Convention Center, March 7–11, 2010.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 473.

The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 496.

The abstracts are reproduced as accepted by the Scientific Program Committee of the Society of Toxicology and appear in numerical sequence.

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