2121 Soluble Nickel-Induced Stem Loop Binding Protein (SLBP) Depletion: A Potential Pathway for Nickel-Mediated Cellular Transformation

A. Jordan, X. Zhang, J. Li, and M. Costa. *New York University, New York, NY.*

Nickel compounds have been established as a group I carcinogen for several decades. Despite over-whelming evidence of nickel compounds' carcinogenicity in humans, the underlying molecular mechanisms that govern nickel induced cellular transformation remain unclear. In this study, we reported that nickel exposure significantly reduced the levels of stem-loop binding protein (SLBP), a protein crucial for canonical histone mRNA metabolism. Consequently, the levels of polyadenated histone H3.1 were increased in nickel-exposed cells. Further studies showed that nickel depleted SLBP by both transcriptional and post-translational regulation. Co-treatment with histone deacetylase inhibitor (sodium butyrate) or DNA methylation inhibitor (5-aza-deoxycytidine) was able to rescue nickel-reduced SLBP mRNA levels, suggesting an involvement of epigenetic regulation. Moreover, nickel-induced depletion of SLBP protein can be reversed by MG-132, the proteasome inhibitor, suggesting SLBP protein degradation is affected by nickel exposure. Taken together, these results suggested that a new mechanism, by which nickel down-regulated SLBP expression and facilitated carcinogenic polyadenation of canonical histone mRNA, might underlie its carcinogenicity.

2122 Potassium Permanganate Use in South Africa: An Ethnopharmacological Profile

R. Street[1], G. Kabera[1,2], and C. Connolly[1]. *[1]South African Medical Research Council, Durban, South Africa; and [2]UNISA, Johannesburg, South Africa.* Sponsor: C. Stewart.

Manganese, in the form of potassium permanganate ($KMnO_4$), is one of the main metals implicated in traditional medicine poisonings in South Africa. Potassium permanganate is widely available; henceforth, its potentially harmful properties may be disregarded. The aim of this study was to determine the prevalence of $KMnO_4$ use in South African traditional medicine by traditional health practitioners (THPs) and describe the practices thereof. Traditional health practitioners (n=201) from KwaZulu-Natal Province of South Africa were interviewed in the local language (isiZulu) by trained interviewers. Information on reasons for using or not using $KMnO_4$, administration methods and modes of administration were collected. It was determined that $KMnO_4$ was used as a constituent of traditional medicine by 158 (79%) of the THPs. Reasons for use included skin rash or wounds (n = 99; 63%) and to treat aches, pains and swelling (n = 74; 47%). Main modes of administration were in the bath (n = 94; 60%), orally (n=67; 42%) and use in herbal compress (n = 66; 42%). Another common mode of $KMnO_4$ administration was via enema, as reported by 28% of the THPs. This study has identified traditional medicine users at risk of manganese toxicity due to commonly used socio-cultural practices. In particular, reports of oral ingestion and use in enema are cause for concern. Based on the information, we conclude that this public health issue needs education programs to enlighten the population against possible harms due to $KMnO_4$ exposure.

2123 Occupational Exposure and Health Effects Investigation of Indium Tin Oxide Workers

S.-H. Liou[1], C.-C. Wang[2], Y.-C. Kuo[1], W.-T. Wu[1], and H.-Y. Liao[1]. *[1]National Health Research Institutes, Miaoli County, Taiwan; and [2]Tri-Service General Hospital, Taipei, Taiwan.* Sponsor: P. Lin.

Due to the rapid development of flat panel and liquid crystal displays (LCD), indium tin oxide (ITO) is increasingly used in the LCD and semiconductor production process. Taiwan was ranked second in the production of large-sized LCD-television panels, which account for 34.7% of the worldwide market. Increasing usage of ITO in Taiwan has been expected to suffer occupational illnesses in these workers. The objectives were to assess the occupational indium exposure in Taiwan, to investigate the relationship between exposure level and the biomarkers of adverse health effects, and to evaluate the health effects of workers for long-term exposure and with job rotation. This study has been approved by IRB of National Health Research Institutes. Environmental and biological monitoring was conducted. The serum indium levels and health effect markers were measured and followed up for three years. The major findings were: 1. The indium exposure levels of total dust measured in one third of work areas in the ITO producing facility (average: 1,462 μg/m^3, range: 166-3,352 μg/m^3) exceeded the TLV of 100 μg/m^3. 2. 36% of subjects in this survey exposed to unacceptable levels of airborne indium in ether total or respirable dust. 3. Over one-third of subjects had serum indium levels (average: 9.12 ppb, range: 3.10-23.2 ppb) higher than biological exposure index (BEI) of 3 ppb. 4. The serum and urine indium levels were found to be strongly correlated to each other (r=0.853). 5. The levels of serum surfactant protein-D (SP-D) and Krebs von den Lungen-6 (KL-6), the adverse lung effects markers, were found to be significantly positively related to both serum and urinary indium levels after adjusted for confounding factors, i.e., age, work duration, and smoking status. 6. The prevalence of workers with an abnormally elevated KL-6 (>500) were significantly elevated in high serum indium group. 7. Significantly positive relationship was found between the level of urinary 8-hydroxydeoxyguanine (8-OHdG), the oxidative damage marker, and the urinary indium level after adjusted for confounding factors. The workers exposed to high level of dust or fume through inhalation may result in adverse effects of lung, such as interstitial pneumonia and pulmonary alveolar proteinosis (PAP).

2124 Hormonal Profile and Trace Metal Contents of Blood and Semen in Men with Infertility Attending the University College Hospital, Ibadan, Nigeria

I. O. Omotosho, J. O. Oladiran, and S. A. Adebayo. *University of Ibadan, Ibadan, Nigeria.*

Male infertility of unknown aetiology have been linked to exposure to environmental and occupational toxic metals; this work investigated exposure to some trace metals and its effect on reproductive hormones in serum and semen. 33 age-matched participants comprising 18 infertile men (cases) and 15 fertile men (controls) were recruited for the study. Follicle Stimulating Hormone (FSH) and testosterone were determined by Enzyme Linked Immunosorbent Assay (ELISA) while Lead (Pb), Cadmium (Cd), Zinc (Zn) and Selenium (Se) were determined using Atomic Absorption Spectrophotometry (AAS) in blood and semen samples from tests and controls. There was no significant difference in median cadmium levels in both serum and seminal plasma samples of cases and controls while decreased median serum Se level (1.14μmol/L) in cases relative to controls (1.92 μmol/L) was observed. Median seminal plasma Zn and Se levels were significantly lower in cases (40.00μmol/L), (0.77μmol/L) than in controls (97.90μmol/L), (1.72μmol/L) respectively. Although median serum FSH was significantly higher in cases (5.84mIU/ml) than in controls (4.44mIU/ml), serum and seminal plasma Se correlated significantly (r=0.843, p=0.000) in cases while serum Se correlated positively (r=0.616, p= 0.006) with testosterone in controls. Zn and Cd correlated significantly in both serum and seminal plasma in controls (r=0.533, p= 0.050 and r=0.611, p= 0.015) and also in serum of cases (r=0.486, p=0.041). Endocrine disruption, hormonal imbalance and induced oxidative stress by trace metals acting as prooxidants may be possible contributory factor to infertility in the studied group.

2125 Pulmonary Toxicity of Gas Metal Arc-Stainless Steel Welding Fume and Component Metals

P. C. Zeidler-Erdely[1], R. Salmen[1], A. Erdely[1], M. Keane[1], V. Kodali[1], J. Antonini[1], and L. Falcone[2]. *[1]NIOSH, Morgantown, WV; and [2]West Virginia University, Morgantown, WV.*

Welding fume is a high-priority agent for further evaluation of lung cancer risk in humans and classified as possibly carcinogenic (Group 2B). Epidemiological studies support a link between welding and lung cancer, particularly stainless steel fume which contains carcinogenic metals like hexavalent chromium and nickel. The objective was to compare the pulmonary toxicity of the individual metal oxide components of gas metal arc-stainless steel welding fume (GMA-SS WF) in A/J mice, a lung tumor susceptible strain. Male A/J mice were exposed by oropharyngeal aspiration to suspensions of GMA-SS WF (1.7 mg) or weight percent equivalent doses found in the total fume of the metal oxide components: chromium (III) oxide/calcium chromate (366 μg/11 μg), nickel (II) oxide (141 μg), or iron (III) oxide (1 mg). Shams were exposed to 50 μl PBS vehicle. Mice were euthanized at 1 d, 7 d, 28 d, and 84 d post-aspiration. Whole lung bronchoalveolar lavage (BAL) was performed to assess pneumotoxicity and macrophages were challenged with Escherichia coli GFP (*E.coli*) for 2 hr at 1:25 multiplicity of infection. At 1 d all components of the welding fume had an effect on macrophages ability to phagocytize bacteria but returned to control levels by 28 d. Notable differences were observed between the toxicity of the total fume and each component metal. Total fume lung cytotoxicity, measured as lactate dehydrogenase levels in acellular BAL fluid, peaked at 7 d. Component cytotoxicity peaked at 1 d then steadily declined. The total GMA-SS WF was more cytotoxic than the sum of the component metals. Analysis of BAL cellular fraction indicated the total fume caused a greater and more persistent inflammatory state (i.e., macrophage and

neutrophil influx) in the lung compared to the metal components. These results suggest the individual metal oxide components of the fume likely have a synergistic influence on lung toxicity and inflammation. In turn, persistent lung inflammation and toxicity of stainless steel WF suggest potential chronic toxicity.

2126 Urinary Metal Concentrations Associated with Shrapnel Fragment Composition in a US Veteran

J. Gaitens[1,2], M. Condon[1], K. Squibb[1,2], and M. McDiarmid[1,2]. *[1]Department of Veterans Affairs Medical Center, Baltimore, MD; and [2]University of Maryland, Baltimore, MD.*

Injuries caused by an Improvised Explosive Device (IED)-related blast or explosion can result in significant wound contamination with foreign debris of unknown composition being deposited throughout soft tissue. The risk of surgical morbidity often precludes removal of these fragments thus raising concern about the potential for long-term toxicant exposure and associated health risks. To better characterize both the local and systemic effects related to retained fragment exposures, the Department of Veterans Affairs established a medical surveillance program that integrates fragment composition data, surrounding tissue analysis and urine biomonitoring outcomes. We present here urine biomonitoring results for 14 metals of concern pre and post-fragment removal for a Veteran who twice underwent surgical fragment excision due to local irritation at the fragment sites. Fragments were then analyzed for composition using energy dispersive x-ray fluorescence (EDXRF). Fragment one, removed six years post-injury was primarily iron (Fe) (>95%) with trace amounts of aluminum (Al) (0.26%) and the second group of fragments, removed 11 years post-injury were primarily zinc (Zn) (44%) and Fe (42%) when analyzed in aggregate. Prior to removal of the second (Zn and Fe) fragment group, urine biomonitoring results indicated all metal concentrations except Zn and tungsten (W) were below established reference values. The elevated Zn level declined significantly after removal of the Zn-containing fragment, implicating the fragment as the likely exposure source. However, the absence of W in removed fragments suggests other potential exposure sources, most likely dietary for the W elevation. This case illustrates the utility of using urine biomonitoring to detect fragment-related metal excursions as well as the complexity of interpreting results as other potential sources of metal exposure must be considered. Long-term biomonitoring and surveillance of Veterans with embedded fragments may help better characterize fragment-related exposures and associated metal body burdens; thus informing the medical management of these individuals and allowing the opportunity for early intervention.

2127 UROtsa As a Model System to Study Metal-Induced Transformation

S. Somji, A. Slusser-Nore, S. H. Garrett, X. D. Zhou, J. R. Dunlevy, K. Zhang, and D. A. Sens. *University of North Dakota, Grand Forks, ND.*

Cadmium and arsenic are environmental toxicants that can induce multiple disease including cancers. The data on the role of cadmium exposure with the development of human cancers is limited, there is epidemiological data that supports a role for cadmium in the development of bladder cancer. Chronic exposures to low concentrations of arsenic have been associated with increased risk for the development of skin, lung and bladder cancer, however the biological processes underlying the ability of inorganic arsenic to transform human cells is unknown. A wide-range of processes have been implicated which include oxidative stress, increased cell proliferation, inhibited DNA repair, genotoxicity, and altered cellular signaling. In order to further determine the role of arsenite and cadmium in the development of bladder cancer, our laboratory has developed an *in vitro* model of bladder cancer by exposing the immortalized, non-tumorigenic urothelial cell line UROtsa to the heavy metals arsenic and cadmium. This has resulted in the generation of six arsenite and the seven cadmium transformed lines that form tumors when injected in immune compromised mice. These tumors show histologic characteristics similar to human urothelial carcinomas with areas displaying prominent squamous differentiation. Global gene analysis of these transformed cell lines has identified genes that are common to both arsenite and cadmium transformed cell lines. In addition, genes were also identified that have carcinogen specific expression patterns. Several genes have been identified (KRT6, SPARC and N-cadherin) and their potential role either in the development or progression of bladder cancers is currently being investigated.

2128 Investigating the Effect of Excess Metals on Sediment Bacterial Communities in the Animas Watershed after the Gold King Mine Breach

K. N. Thompson, J. E. Wilkinson, L. L. Hensley, P. N. Smith, and G. D. Mayer. *Texas Tech University, Lubbock, TX.*

On August 5, 2015 a levee at the Gold King Mine was breached when EPA contractors attempted to add a tap to stem the leakage of acid mine water. As a result, the mine drained approximately 3 million gallons of acid mine waste into the Animas River Watershed. The plume of metal-contaminated water traveled from the mine to Cement Creek, where a majority of the larger sediment particulates were deposited. The yellow-brown water continued to the Animas and San Juan Rivers before being deposited into Lake Powell in Utah. The EPA listed iron, cadmium, lead, arsenic, zinc, and copper as metals of concern after the spill. Presumably, many of these metals were adsorbed to sediments as they traveled through the Animas River Watershed. Increased levels of metals would add a selective pressure on the communities of bacteria inhabiting the sediments downstream of the mine. Because sediment samples from before the breach were not available, we compared the contaminated sites to control sites of the Animas upstream of the confluence with Cement Creek, and the San Juan upstream of the confluence with the Animas. To study population diversity and structure of sediment-borne bacterial communities, we used 16S amplicon sequencing for bacterial taxonomic identification. Additionally, we investigated how the function of these communities shifted by studying the abundance, distribution and activity of metal resistance and DNA repair genes. Finally, we tested the ability of bacteria collected from the Animas and Cement Creek locations to resist metal toxicity. We found that the three sample locations closest to the mine had decreased alpha and increased beta diversity when compared to all other samples in the Animas River Watershed. Bacterial composition of the communities closest to the mine also shifted. The most abundant bacteria in sediments closest to the mine was *Gallionella sp.*, an iron oxidizing species of bacteria. Loss of diversity in an ecosystem would limit the ability of the ecosystem to recover from further perturbations, whether natural or anthropogenic. However, the sediment communities did shift towards bacteria that would be better able to process excess iron and other metals in the acid mine drainage.

2129 Single Cell Cisplatin and Other Metal Measurements by ICP-MS

L. Amable[1], and C. Stephan[2]. *[1]National Institute on Minority Health and Health Disparities, Bethesda, MD; and [2]Perkin Elmer, Shelton, CT.*

Metal balance in humans is crucial and complex for the maintenance of health. Exposure to metals has been implicated in a variety of diseases such as cancer, yet metals are essential for the proper functioning of enzymes and proteins. The measurement of metals at the level of a single cell is difficult, as traditional methods do not convey the distribution and individual cellular variation. Here, we present a new method, Single Cell-Inductively Coupled Plasma-Mass Spectrometry (SC-ICP-MS), to quantitate the metal concentration within individual cells. The method was developed in ovarian cancer cells using the chemotherapy drug, cisplatin. Cisplatin and other platinum-containing compounds are the most widely used class of cancer chemotherapy drugs in the Western world. Many patients initially respond to therapy, however later patients relapse and are resistant to further cisplatin therapy. One of the mechanisms of cisplatin resistance includes decreased cellular cisplatin uptake. Time course experiments were performed to measure the change of cisplatin uptake over time using the A2780 cisplatin-sensitive and the corresponding cisplatin-resistant A2780-CP70 ovarian cancer cell lines. Individual cellular cisplatin levels were collected and a histogram representing the cell population was generated using the Syngistix Single Cell Application. In accordance with previous studies, the results show that the cisplatin sensitive cells accumulated more platinum in comparison to the cisplatin resistant cells. A heterogeneous distribution of cisplatin within the cellular population was observed, reflecting cisplatin uptake differs from cell to cell. Even after 8 hours of exposure, there was a significant number of cells that had low levels of intracellular cisplatin. Cellular concentrations of zinc, iron, and copper were successfully analyzed by SC-ICP-MS. The heterogeneous distribution of these metals were also observed, however there were no large differences between cell lines overall. In conclusion, single cell ICP-MS analysis allows for the quantitation of cisplatin, as well as other metals, within individual cells. New strategies to increase cisplatin uptake within cancer cells can be developed by SC-ICP-MS, translating to better clinical responses. Utilization of this technique can be applied to other areas of metal-based research in biological systems.


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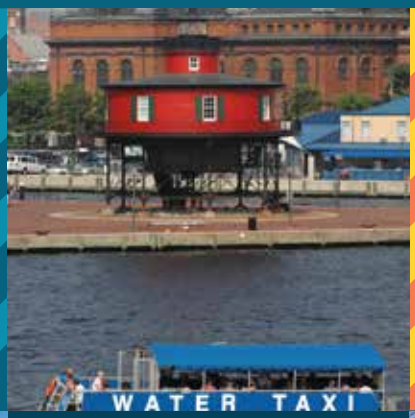

OXFORD
UNIVERSITY PRESS

ISSN 1096-6080
Volume 156, Issue 1
March 2017

www.toxsci.oxfordjournals.org

The Official Journal of the Society of Toxicology

SOT | Society of Toxicology

www.toxicology.org