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The 10th Conference on Metal Toxicity and Carcinogenesis: Overview and Recent Advances

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Abstract

Environmental and occupational metal exposures promote numerous diseases including cardiovascular, pulmonary and neurological disorders as well as various types of cancers. Research in metal toxicity and carcinogenesis focuses on addressing major health concerns associated with metal exposure. In October 2018, the 10th Conference on Metal Toxicity and Carcinogenesis held in Albuquerque, New Mexico, assembled scientists from across the United States to discuss current status and future directions in this unique and important field of research. Here, we summarize the on-going research and recent advances presented at this conference and provide insights on future progression and challenges of the field.

Keywords

metals; toxicity; carcinogenesis

Introduction

Toxic metals, such as arsenic, chromium, lead, mercury, cadmium, uranium, and various others are global health concerns. Environmental and occupational metal exposures are linked to a myriad of diseases and cancers. Every other year, scientists from academia, industry, and government gather to discuss research efforts in the field of metal toxicity and carcinogenesis (1–4). In October 2018, the 10th biennial conference was held in Albuquerque, New Mexico, marking 18 years of the conference series which began in 2001. Over 150 attendees including faculty, staff, postdocs, and students assembled to exchange information and discuss up-and-coming research topics. The conference contained 10 scientific sessions of presentations with more than 50 speakers, a poster session with over 60 posters, and a special session on grant and career development with keynote speakers from

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Conflict of interest

The authors declare no conflict of interest

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the National Institutes of Health. Here, we summarize the research presented at the conference and highlight the latest work by conference attendees in this special issue of *Toxicology and Applied Pharmacology*.

Summary of Scientific Sessions

The first session was opened by a keynote lecture from Bernardo Lemos (Harvard TH Chan School of Public Health). He presented work delineating how chromium exposure triggers amplification of rDNA and discussed the use of DNA methylation as a marker for aging. Following the talk by Bernardo Lemos, Matthew Campen (University of New Mexico) presented work performed by his lab in Blue Gap Tachee, AZ where they identified significant uranium and vanadium contamination and determined that particulate matter arising from rural windblown dust was substantially more toxic in terms of acute inflammation and injury in the lung. Thereafter, Veena Antony (University of Alabama at Birmingham) presented work on airway remodeling and COPD induced by cadmium and discussed inhibition of PAD2 as a potential means to block COPD progression. Tiffany Sanchez (Columbia University) then discussed her work on measuring various parameters in the urine to identify common environmental sources of exposure among a semi-rural Bangladesh population. Otto Appenzeller (University of New Mexico) discussed the historical use of arsenic as a therapeutic agent for Syphilis and Alicia Bolt (University of New Mexico) presented her recent research on uranium immunotoxicity reporting that iron supplementation may alter uranium accumulation. Bing-Hua Jiang (University of Iowa) then presented his work highlighting chromium induction of malignant transformation and tumor angiogenesis with a special focus on a novel mechanism of microRNA suppression and DNA methylation.

The second session started with a keynote presentation by Koren Mann (McGill University, Canada) delineating the mechanisms by which methylated arsenicals have the potential to alter plaque composition in a murine atherosclerosis models with a more pronounce effect observed in males. Thereafter, Malek El Muayed (Northwestern University) reported a significant association between age, gender, and islet cadmium level, highlighting the endocrinotoxicity of cadmium. Next, Rama Gullapalli (University of New Mexico) discussed cadmium carcinogenesis and his work dissecting the underlying mechanism of gallbladder cancer through dysregulated PI3K-Akt signaling in gallbladder epithelium. Anatoly Zhitkovich (Brown University) then presented his findings pinpointing the reductive metabolism of chromium(VI) as the key factor modulating its carcinogenic potency. Yan Shu from the University of Maryland presented his work identifying cadmium as a previously unrecognized factor for the broad variation in drug disposition and response through regulating transporter protein activity. Presenting his work from the University of Hong Kong, Jiangang Shen discussed how the traditional medicine Angong Niu Huang pills, along with metal elements, could be used as an adjunct therapy to reduce hemorrhagic transformation and improve outcome in ischemic stroke with delayed t-PA treatment. Finishing up the session, Sakhila Banu (Texas A&M University) presented her work on alterations of the placental vasculature through chromium(VI), including chromium-induced placental/fetal blood flow restriction and subsequent intrauterine fetal growth impairment.

The keynote speaker Clark Lantz (University of Arizona) started the third session by discussing the effects of early-life inhalation exposure to arsenic-containing dust on lung development. Next, Zhifeng Qi (Capital Medical University, China) discussed her work identifying a novel zinc-dependent mechanism of cerebral ischemia-induced blood-brain barrier damage. Walter Watson from the University of Louisville then presented his work highlighting sex-dependent variations of arsenic exposure in a non-alcoholic fatty liver disease model and James Wise (University of Kentucky) showed that chromium(VI) transformation *in vitro* increases lipid metabolism without inducing anaerobic glycolysis. Jamie Young (University of Louisville) presented her work identifying that both cadmium and high-fat diet significantly and independently affect levels of essential metals in the blood, kidney, and liver. Valerie Minarchick (University of Colorado) presented her current research describing differential effects of oxidized and reduced zinc oxide nanoparticles on microvascular reactivity and activation. To complete the session, Rong Pan from the University of New Mexico presented a mechanism of brain damage induced by intracerebral hemorrhage through ferrochelatase-mediated formation of zinc protoporphyrin.

The fourth session was opened by the keynote presentation by Marcelo Bonini (Medical College of Wisconsin), which focused on the role of inorganic arsenic exposure in promoting the development of hard-to-treat breast cancer subtypes with increased morbidity. Astrid Engel (Tulane University) then presented her work identifying cadmium or nickel exposures as promoters of retrotransplantation of endogenous L1 elements, a mutagen residing in the human genome. From the University of Kentucky, Lei Wang reported that transcription factor EB could be an important factor involved in arsenic induced reproductive issues. Chuanshu Huang (New York University) then presented research detailing the mechanism of nickel-induced lung carcinogenesis whereby DNMT3b overexpression mediates long noncoding RNA downregulation. To end the session, Chendil Damodaran (University of Louisville) discussed the landscape and mechanism of cadmium induced prostate carcinogenesis followed by Max Costa (New York University) presenting his work on epigenetic mechanisms of arsenic carcinogenesis through polyadenylation of canonical histone mRNA.

The fifth session was started by keynote speaker John Wise (University of Louisville), talking about chromosome instability in chromium(VI) carcinogenesis. Switching gears to focus on technical elements of metals analysis, Mehdi Ali (University of New Mexico) discussed biological sample preparation and analysis of trace metals using inductively coupled plasma mass spectrometry. Thereafter, Dazhong Xu (New York Medical College) presented work on a mechanism of chromium carcinogenesis on Gene 33 (Mig6, ERFF11) and regulation of DNA damage response. Suresh Cuddapah (New York University) then reported that mercury and 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD) co-exposure alters the epigenome which was followed by Xuefeng Ren (University at Buffalo) who presented research on multi-generational impacts of arsenic exposure on genome-wide DNA methylation, skin lesions and carcinogenesis. Along the theme of transgenerational inheritance, Vamsi Gangaraju (Medical University of South Carolina) then presented research detailing the transgenerational developmental defects and hyperplasia caused by chromium(VI) exposure using the *Drosophila* model system. Finally, Fei Chen (Wayne State

University) finished the session with a presentation on a mineral dust-induced gene which acts as an antagonist for the inhibitory histone methylation markers.

Session six started with a keynote presentation by Shuk-Mei Ho (University of Cincinnati), focusing on arsenic and lead carcinogenesis through the disruption of epithelial stem-like cell populations. Next, Kurt Zhang (Texas A&M University) presented his work on ventricular noncompaction induction by prenatal cadmium exposure and Chunyuan Jin (New York University) then discussed inhibition of chromatin assembly as a new mechanism of metal toxicity. Sarah Michel (University of Maryland) discussed her initial work testing the hypothesis that cadmium and gold mediate the inflammatory response by targeting and altering the activity of zinc finger proteins in inflammatory pathways. Following this, Ana Cardoso (University of Louisville) presented data identifying a mechanism of arsenic-induced chromosome instability through dysregulation of cell cycle proteins. Zhishan Wang (University of Kentucky) then gave a presentation on the synergistic lung tumorigenesis effect of arsenic and benzo(a)pyrene in mice and Anuradha Mudipalli (United States Environmental Protection Agency) concluded the session by providing a comprehensive overview of iron toxicity in the etiology of breast cancer.

For session seven, following the tradition of past conferences, this year's conference also included a special grant workshop session where speakers from two NIH funding agencies gave presentations on grant and career development and were available both directly after their talks and during session breaks to discuss several aspects of NIH funding mechanisms. The speakers for this year's session included Leroy Worth (National Institute for Environmental Health Sciences), Fred Tyson (National Institute for Environmental Health Sciences), and Konstantin Salnikow (National Cancer Institute). Topics ranged from grantsmanship to the interworking funding applications to review processes. This is a very beneficial and informative workshop for all participants but particularly early-stage investigators.

Session eight was a special session which focused on population health. For this session, Johnnie Lewis (University of New Mexico) presented an on-going study on the effects of metal mixture exposures on preterm birth, inflammation, and immune dysregulation, as well as potential long-term neurotoxicity. Todd Everson (Emory University) reported that metal-associated epigenetic differences have implications for fetal growth and neurodevelopment. Thereafter, Rebecca Fry (University of North Carolina at Chapel Hill) showed that the placenta may serve as a source of exposure for toxic substances and drive the development of specific diseases later in life. As the last speaker of the session, Ana Navas-Acien (Columbia University) discussed the contributions of early life and chronic metal mixture exposures to birth outcomes, development, and adult disease.

The ninth session was started by Mirek Styblo (University of North Carolina at Chapel Hill), presenting his work on mouse models for arsenic toxicity with a focus on arsenic interference in metabolism pathways. Thereafter, Chengfeng Yang (University of Kentucky) presented research illustrating the ability of microRNA-494 to suppress chromium(VI)-induced cell transformation through c-Myc down-regulation. Alan Parrish (University of Missouri) then gave a talk on his work delineating how cadmium and lead may promote

metastasis of renal cell carcinoma. Jinhui Li (University of Hong Kong & New York University) discussed a population study on coal mines and lung cancer mortality followed by Carlyle Ducheneaux (Cheyenne River Sioux Tribe) presenting information gained from on-going risk assessment research involving the Cheyenne River Sioux Tribe. Concluding the session, Kun Lu (University of North Carolina at Chapel Hill) presented work on the regulation of arsenic-induced LXR/RXR signaling perturbation by gut microbiota followed by Yinsheng Wang (University of California Riverside) who discussed the characterization of RING finger proteins as arsenic targets.

The last session of the conference was started by the keynote lecture from John Vincent (University of Alabama), about the precise mechanism and current research on chromium(III) binding with DNA. Xixi Zhou (University of New Mexico) presented his work describing arsenic trioxide as a potential anti-metastatic agent for the treatment of head and neck squamous carcinoma. Joseph Landolph, Jr (University of Southern California) presented molecular mechanisms of genotoxicity for insoluble nickel compounds. Sebastian Medina (University of New Mexico) then reported recent progress on mechanisms of arsenic hematotoxicity. Thereafter, Aikseng Ooi (University of Arizona) discussed the role of iron signaling in hereditary leiomyomatosis and renal cell cancer followed by Jonathan Freedman (University of Louisville) who discussed gender difference in response to cadmium exposure and high-fat diet. The final speaker of the conference, J. Christopher States (University of Louisville), presented recent advances on RNA expression analysis for investigations into the mechanisms of low-level and chronic arsenic exposure-induced carcinogenesis.

Concluding Remarks, Challenges, and Future Directions

The 10th conference of metal toxicity and carcinogenesis brought together a community of metal researchers from across the country. The premier conference of this field focused on 1) the mechanisms of metal-induced toxicity and cancer; 2) strategies for risk assessment, prevention, and intervention; 3) translation from basic research to clinical application or public policy. From the presentations and discussions that occurred during the conference, we believe there are several up-and-coming hot topics of research, including, but not limited to: metal mixtures and mixed exposures, -omics approaches for mechanistic studies, particulate/insoluble forms of metal exposure, population studies on risk assessment and health outcomes, and chemical mechanisms of metal interacting with biomolecules. Another major takeaway from this conference are the current research challenges in the field of metals research including developing pathways to connect mechanistic research to community intervention, translating risk assessment and mechanisms of metal exposure into prevention strategies, and developing efficient bioanalytical approaches for assessing the impact of metal and metal mixture exposures through basic research. These current challenges along with other gaps of knowledge discussed during the conference highlight not only future directions of the field but also several opportunities to expand the impact of current research. In conclusion, the conference successfully supported interactions between scientists with a shared research focus and helped move the field forward by presenting and discussing recent advances in metals research. This special issue of Toxicology and Applied Pharmacology highlights recent research in metal toxicity and carcinogenesis by the attendees of the conference.

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