The 7th Asian Congress on Environmental Mutagens (ACEM)
The 19th Chinese Environmental Mutagen Society Meeting (CEMS)

The Impact of Global Change on Asian Environment and Genomic Health

CONFERENCE BROCHURE

November 4–7, 2022
Qingdao China

Welcome Message

Dear colleagues,

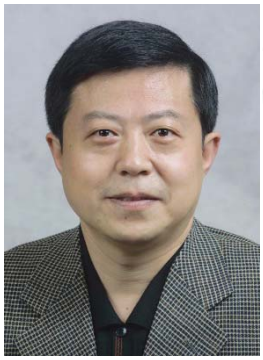
As president of the Asian Environmental Mutagen Association (AAEMS), I am pleased to welcome you to the 7th Asian Conference on Environmental Mutagens (7th ACEM) and the 19th Conference of Chinese Environmental Mutagen Society (19th CEMS) held in Qingdao on November 4-7, 2022.
With a theme of "Global Change and Environmental Genomic Health in Asia", the conference aims to promote research on the basic application and transformation of environmental mutagens and genomic health in Asia and the Pacific Rim, and to develop and close to peer exchanges and cooperation within the region. The conference was originally scheduled to be held in Qingdao in November 2021. However, we are sorry that the conference had to be postponed until November 4-7, 2022 given the COVID-19 pandemic.

The Asia-Pacific region has assumed a critical role in the global economy. AAEMS is composed of eight members of countries. Although every country has its own different cultural model and economic development level, we face common environmental and health problems. The AAEMS was established to promote the continuous expansion and orderly conduct of research activities and exchanges in the field of environment and health.

The topics of the conference include not only traditional fields such as DNA damage repair, chemical carcinogenesis, teratogenesis, and mutagenesis, but also some new fields such as exposure science and exposure omics, genomics and epigenetics, computer modeling, and bioinformatics. We hope that this conference will attract the active participation of scholars from various fields of environment and health sciences, especially young scholars and students, so as to inject fresh vitality into our field.

The Chinese Environmental Mutagen Society (CEMS) as the organizer of the conference, it has made a great effort to organize the conference. In face of COVID-19, CEMS has repeatedly coordinated with various countries to adjust the time of conference, so that as many participants as possible can attend the conference. In view of China's current situation and policies in mitigating COVID-19, the conference plans to be held both online and offline. The vast majority of foreign representatives are likely to attend the conference online. However, we will still strive to ensure the best conference possible.

Finally, I wish this conference a great success.



Prof. Jia Cao

Chairman of ACEM/CEMS 2022
President of AAEMS
President of CEMS

Congress Date and Venue

Date: November 5 - 6, 2022

Schedule outline:

November 5	**Morning: Opening Ceremony & Keynote Lectures** **Afternoon: Symposium**
November 6	**Morning: Symposium** **Afternoon: Keynote Lectures & Closing Ceremony**

Notice

1. The keynote lectures and symposia in English will be held during November 5-6, 2022 online as scheduled and symposia in Chinese on-site has been postponed. The working language of the congress is **English**.

2. **ONLY** the registered participants, speakers, and invited members are allowed to join the online meeting. We will send the information to your mailbox. To join the meeting, please click **Join Zoom Meeting** and type the unique passcode.

Committees

Organizations

Asian Association of Environmental Mutagen Societies (AAEMS)

Chinese Environment Mutagen Society (CEMS)

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School of Public Health, Qingdao University

School of Public Health, Sun Yat-sen University

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Program at a glance

Program Overview

Saturday, November 5, 2022	
8:40-9:00	**Opening Remarks**
9:00-10:40	**Keynote Lecture (KL)**
10:40-10:55	Coffee Break
10:55-12:20	**Keynote Lecture (KL)**
12:20-14:00	Lunch Break
14:00-15:40	**Symposium 1 (S1)**
15:40-15:55	Coffee Break
15:55-17:30	**Symposium 1 (S1)**

Sunday, November 6, 2022	
8:30-10:10	**Symposium 2 (S2)**
10:10-10:25	Coffee Break
10:25-12:05	**Symposium 2 (S2)**
12:05-14:00	Lunch Break
14:00-15:40	**Keynote Lecture (KL)**
15:40-15:55	Coffee Break
15:55-17:35	**Keynote Lecture (KL)**
17:35-18:00	**Closing Remarks**

Scientific Program

Opening Remarks/Keynote Lecture

Saturday, November 5, 2022	
8:40-9:00	**Opening Remarks** **Chair: Prof. Jia Cao**
	Keynote Lecture (KL) **Chairs: Prof. Yuepu Pu, Prof. Weidong Qu**
9:00-9:50	**KL-1** How AI Can Beat Animal Testing at Finding Toxic Chemicals as Potential Carcinogen. **Prof. Thomas Hartung** (Johns Hopkins University, United States)
9:50-10:40	**KL-2** A Body Map of Somatic Mutagenesis in Morphologically Normal Human Tissues. **Academician Dongxin Lin** (Chinese Academy of Medical Sciences, China)
10:40-10:55	**Coffee Break**
10:55-11:45	**KL-3** The Future of Genome Research in Asia. **Prof. Masami Yamada** (National Defense Academy, Japan)
11:45-12:20	**KL-4** Applying an Integrative Approach for Risk Assessment on The Effects of Chemical Mixtures in The Context of Real-Life Risk Simulation. **Academician Aristides M. Tsatsakis & Dr. Elisavet Renieri** (University of Crete, Greece)
12:20-14:00	**Lunch Break**

Symposium 1

Saturday, November 5, 2022	
	Symposium 1 (S1) **Chairs: Prof. Yankai Xia, Prof. Yuanyuan Xu**
14:00-14:25	**S1-1** DNA Adductomics in Human Tissues. **Prof. Haruhiko Sugimura** (Hamamatsu University, Japan)
14:25-14:50	**S1-2** Discovery of Functional Link between DNA Double-strand Break Repair and the Early Transcriptional Response to the Sex Hormone. **Prof. Shunichi Takeda** (Shenzhen University, China)
14:50-15:15	**S1-3** Paternal Environmental Stress: From Sperm Epigenome to Offspring Synapse Organization. **Prof. Yankai Xia** (Nanjing Medical University, China)
15:15-15:40	**S1-4** The Emerging Role of Nfe2l1 in Carcinogenesis: Action as and Beyond a Transcription Factor. **Prof. Yuanyuan Xu** (China Medical University, China)
15:40-15:55	**Coffee Break**
	Symposium (S1) **Chairs: Prof. Nan Sang, Prof. Yanhong Wei**
15:55-16:15	**S1-5** Enhanced Gastric Tumorigenesis by Accumulation of Tumor-Associated Macrophage in the Absence of Histamine Signal. **Prof. Ki Taek Nam** (Yonsei University, Korea)
16:15-16:40	**S1-6** Maternal Cadmium Exposure During Gestation Impairs Hippocampal Neurogenesis and Cognition via Reducing Placenta-Derived Estrogen in Offspring. **Prof. Hua Wang** (Anhui Medical University, China)
16:40-17:05	**S1-7** The Cardiovascular Toxicity of Aryl Organophosphate Flame Retardants in Embryonic Development. **Prof. Yanhong Wei** (Sun Yat-sen University, China)
17:05-17:30	**S1-8** Injury Target, Toxic Effect and Molecular Mechanism of Atmospheric Pollutants from Coal-Burning Area. **Prof. Nan Sang** (Shanxi University, China)

Symposium 2

Sunday, November 6, 2022	
	Symposium 2 (S2) **Charis: Prof. Dianke Yu, Prof. Da Chen**
8:30-8:55	**S2-1** QSAR Prediction of Ames Mutagenicity. **Dr. Kiyohiro Hashimoto** (Takeda Pharmaceutical, Japan)
8:55-9:20	**S2-2** A Toxicity Pathway-Based Approach to Develop Adverse Outcome Pathway. **Prof. Dianke Yu** (Qingdao University, China)
9:20-9:45	**S2-3** Development of Physiologically Based Pharmacokinetic (PBPK) Models Within Bayesian Framework for Perfluorooctane Sulfonate (PFOS) and Its Implications in the Derivation of Health-Based Toxicity Values. **Research Assistant Prof. Wei-Chun Chou** (University of Florida, United States)
9:45-10:10	**S2-4** Analytical Development for Environmental Exposome Research. **Prof. Da Chen** (Jinan University, China)
10:10-10:25	**Coffee Break**
	Symposium 2 (S2) **Chairs: Prof. Yang Luan, Prof. Tiantian Li**
10:25-10:50	**S2-5** Metabolic Mechanisms and Toxic Effects of Polycyclic Aromatic Hydrocarbons Regulated by CYP Enzymes Under Combined Pollution. **Associate Prof. Kai Luo** (Southeast University, China)
10:50-11:15	**S2-6** Applying Multi-Omics Approach to Reveal the Lung Cancer Biomarker. **Associate Prof. Ting Xiao** (Chinese Academy of Medical Sciences and Peking Union Medical College, China)
11:15-11:40	**S2-7** Airborne $PM_{2.5}$ Exposome and Cardiovascular Health: A Population-based Integrated Methodology Establishment and Application. **Prof. Tiantian Li** (Chinese Center for Disease Control and Prevention, China)
11:40-12:05	**S2-8** Integrated-Studies Interpreted Oligophagous Butterfly Tolerate to Strong Mutagen Aristolochic Acids. **Prof. Yang Luan** (Shanghai Jiao Tong University, China)
12:05-14:00	**Lunch Break**

Keynote Lecture/Closing Remarks

Sunday, November 6, 2022	
	Keynote Lecture (KL) **Chairs: Prof. Shuangqing Peng, Prof. Jun Yang**
14:00-14:50	**KL-5** Effects of Circulating Small Extracellular Vesicle on Cancer Metastasis and Chemoresistance. **Prof. Keon Wook Kang** (Seoul National University, Korea)
14:50-15:40	**KL-6** Air Pollution Exposure Mitigation and Health Intervention: Insights from Source-Specific Cardiorespiratory Impairments. **Prof. Wei Huang** (Peking University, China)
15:40-15:55	**Coffee Break**
15:55-16:45	**KL-7** IARC Monographs on the Identification of Carcinogenic Hazards to Humans. **Dr. Federica Madia** (The International Agency for Research on Cancer (IARC), France)
16:45-17:35	**KL-8** DNA Demethylation and Environmental Health Effects. **Prof. Hailin Wang** (Chinese Academy of Sciences, China)
17:35-18:00	**Closing Remarks** **Chair: Prof. Jia Cao**

Introduction of Invited Speakers (Keynote Lecture)

KL-1

How AI Can Beat Animal Testing at Finding Toxic Chemicals as Potential Carcinogen.

Prof. Thomas Hartung

Johns Hopkins University, United States

Biography

Thomas Hartung, MD, PhD, is the Doerenkamp-Zbinden-Chair for Evidence-based Toxicology in the Department of Environmental Health and Engineering at Johns Hopkins Bloomberg School of Public Health, Baltimore, with a joint appointment at the Whiting School of Engineering. He also holds a joint appointment for Molecular Microbiology and Immunology at the Bloomberg School. He is adjunct affiliate professor at Georgetown University, Washington D.C.. In addition, he holds a joint appointment as Professor for Pharmacology and Toxicology at University of Konstanz, Germany. He also is Director of Centers for Alternatives to Animal Testing (CAAT, http://caat.jhsph.edu) of both universities. CAAT hosts the secretariat of the Evidence-based Toxicology Collaboration (http://www.ebtox.org) and manages collaborative programs on Good Read-Across Practice, Good Cell Culture Practice, Green Toxicology, Developmental Neurotoxicity, Developmental Immunotoxicity, Microphysiological Systems and Refinement. As PI, he headed the Human Toxome project funded as an NIH Transformative Research Grant and the series of annual Microphysiological Systems World Summits starting in 2022 by 52 organizations. He is Field Chief Editor of *Frontiers in Artificial Intelligence*. He is the former Head of the European Commissions' Center for the Validation of Alternative Methods (ECVAM), Ispra, Italy, and has authored more than 620 scientific publications with more than 41,000 citations (h-index 105). His toxicology classes on COURSERA had more than 15,000 active learners.

Abstract

A number of high-content and high-throughput technologies as well as the curation of databases of legacy data and scientific publications have made big data in toxicology available in recent years. Machine learning (artificial intelligence, A.I.) allows to mine these data and make “big sense” from these big data providing novel tools to complement risk assessments. We created a large toxicological data base from

the European Chemical Agency (ECHA) extracting using linguistic search engines into a structured, machine readable and searchable database. Adding further public databases, a read-across-based structure activity relationship (RASAR) was developed. Predictions were validated by cross-validation.

In collaboration with Underwriters Laboratories (UL), a global safety consulting and certification company, a database with more than 10 million chemical structures (more than 300,000 of which annotated with biological and chemicophysical data and 80,000 with animal data). It took an Amazon cloud server two days to analyze the similarities and differences between the 10 million chemicals to place them on a map, where similar chemicals are put close to each other, dissimilar ones distant. Making use of 74 properties in a data fusion approach, random forest machine learning was applied in a five-fold cross-validation. Applying this to 190,000 classified chemicals based on animal tests, 87% of the time the computer was correct. Notably, each prediction comes with an expression of certainty based on the constellation of data available. The software was even better for finding toxic than non-toxic substances with 89% success—exceeding the 70 percent probability of animal tests to find a toxic substance again in a repeat animal test, shown in a parallel analysis of the database. The software (the UL Cheminformatics Tool Kit) at this stage predicts nine different hazard classifications, traditional testing for which consumes 57 percent of all animals in safety testing in Europe, or about 600,000 animals per year.

The predicted endpoints include mutagenicity but other elements possibly contributing to an integrated strategy to replace the cancer bioassay seem possible. In the process of expanding the RASAR approach to systemic toxicities, ongoing work is aiming also to predict directly the outcome of the cancer bioassay with promising preliminary results. Other A.I. uses will be discussed.

KL-2

A Body Map of Somatic Mutagenesis in Morphologically Normal Human Tissues.

Academician Dongxin Lin

Chinese Academy of Medical Sciences, China

Biography

Dr. Dongxin Lin is professor and director of the Department of Etiology and Carcinogenesis, Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union medical College. He is also professor of Sun Yat-sen University Cancer Center. He is an academician of Chinese Academy of

Engineering. His major research interests are cancer genetics and genomics, focusing on the identification of germline and somatic genomic alterations that are associated with the development and progression of human cancers such as esophageal cancer and pancreatic cancer. He has published more than 300 research papers in peer-review journals including *Nature*, *Nat Genet*, *Nat Med*, *Nat Commun*, *Gastroenterology and Cancer Res*, with H-index of 88 in 2022.

Abstract

Somatic mutations occur naturally in normal cells during cell division. The accumulation of such mutations in normal tissues are associated with aging and disease. Numerous studies have shown that cancer cells have a large somatic mutation burden, which can be attributable to the endogenous and/or exogenous mutagens. We have performed a comprehensive genomic analysis of 1,737 morphologically normal tissue biopsies of 9 organs from 5 donors. We found that somatic mutation accumulations and clonal expansions were widespread, although to variable extents, in morphologically normal human tissues. Somatic copy number alterations were rarely detected, except for in tissues from the esophagus and cardia. Endogenous mutational processes with the SBS1 and SBS5 mutational signatures are ubiquitous among normal tissues, although they exhibit different relative activities. Exogenous mutational processes operate in multiple tissues from the same donor. We reconstructed the spatial somatic clonal architecture with sub-millimeter resolution. In the esophagus and cardia, macroscopic somatic clones that expanded to hundreds of micrometers were frequently seen, whereas in tissues such as the colon, rectum and duodenum, somatic clones were microscopic in size and evolved independently, possibly restricted by local tissue microstructures. Our study depicts a body map of somatic mutations and clonal expansions from the same individual.

KL-3

The Future of Genome Research in Asia.

Prof. Masami Yamada

National Defense Academy, Japan

Biography

After spending 27 years in National institute of Health Sciences, Professor Masami Yamada currently teaches Chemistry, Biology and Genetic Engineering at National Defense Academy of Japan. Graduation

from Osaka University Faculty of Pharmaceutical Sciences with a Master's degree in 1986, she trained in microbial genetics and molecular biology using Escherichia coli under Professor Atsuo Nakata at the Institute of Microbial Diseases, School of Medicine, and wrote her degree thesis on the regulatory mechanisms of phosphate regulons, then received her Ph.D. degree. Soon after, she became a research staff in Division of Genetics and Mutagenesis of National Institute of Health Science, NIHS, in 1990. Together with Dr. Takehiko Nohmi, she worked on the improvement of Ames tester strains and the development of the target gene and its recovery system for transgenic mice used in genotoxicity testing. In 1995, she went to the UK and spent one year at the Clare Hall Laboratories as an overseas fellow of Science and Technology Agency (at that time). She worked with Dr. Peter Karran on a mechanism to recognize cisplatin and DNA cross-links by mismatch repair proteins, which resulted in a paper. After returning to Japan, she contributed to the discovery of translesion DNA polymerase in E. coli. She published nearly hundred papers listed in SCOPUS and h-index is 27. Using genetic engineering techniques, she has constructed many strains from standard tester strains for the Ames. Such strains are useful for research fields on environmental mutagens. Strain requests come to her every year from domestic, Asia, Europe, North America, South America, and other countries. She has been a member of the Japanese Environmental Mutagen and Genome Society, JEMS, since she joined the NIHS, and was awarded a JEMS Encouragement Award in 1998. She has served as an editorial board member, councilor, and director, and has been the editor-in-chief for the society's journal, *Genes and Environment* since 2018. She served as Treasurer of the International Association of Environmental Mutagenesis and Genomics Society for 2013 - 2017. She is also currently serving as President of JEMS and working to reform the Society.

Abstract

As President of JEMS, I would like to introduce three recent achievements in genome research in Japan: First, Hawk-Seq, a new technology developed by Matsumura's group, that can systematically and more accurately detect mutations that may lead to cancer. Second, Totsuka's group has developed a powerful method to identify cancer-causing environmental mutagens by combining adductome and mutation signatures. The third, identified by Suzuki's group, is an examination of the dangers of genome disruption leading to chromothripsis that may be caused by genome editing. Matsumura's group (Kao Corporation, Kawasaki) has developed a new methodology called Hawk-Seq, which uses next-generation sequencing (NGS) to directly detect mutagens that induce genome-wide mutations. This may help to understand mutagen-induced mutation signatures and ultimately, the relationships between mutagens and human cancer. Since the frequency of mutations due to exposure to mutagens is very low, it is important toimprove the sequencing accuracy of NGS to detect mutagen-induced mutations. Therefore, they developed an error correcting sequencing (ECS) to reduce the error frequency in NGS analysis: which collects sequence

information from both strands of a dsDNA fragment and can distinguish between true mutations and sequence errors. The ECS reduced error frequency to about $1/10^7$ for GC base pairs and $1/10^8$ for AT base pairs. Hawk-Seq was also effective in elucidating 96D mutation signatures caused by mutagen exposure and a close association between mutagens and human cancers.

Totsuka's group (Nihon University & National Cancer Center Research Institute, Tokyo) identified the etiology of frequently occurring esophageal cancer in the Ci Xian high-risk area of China by a combination of adductome and mutation signature analyses. They collected surgical specimen of esophageal cancer patients in the high-risk area and compared them with those from low-risk areas. The results suggested that the guanine adduct of N-nitrosopiperidine (NPIP) was the cause of esophageal cancer in the Ci Xian area. They then analyzed the genome in esophageal cancer cells that developed in rats after NPIP administration. A reasonable match was found in the mutation signature between the samples from the NPIP-treated rats and those from the cancer patients in Ci Xian mentioned above. Finally, I will address the concerns of Suzuki's group (National Institute of Health Sciences, Kawasaki) about the “on-target” toxicity of the Crisper/Cas9. Genome editing with CRISPR/Cas9 begins with double-stranded breaks, which are repaired by non-homologous end joining in humans, during which mutations are likely to be introduced. Therefore, concerns about genotoxicity have been mentioned for CRISPR/Cas9-based therapies. It has recently been reported that chromothripsis has been observed in more than 50% of some cancer types. Suzuki et al. created “designed” translocations by genome editing. They found that about 1 to 2% of translocations together with about 20 % of chromosome aberrations involving the targeted chromosomes immediately after genome editing. These results suggest that the risk of genome editing is higher than expected. They warn against the use of genome editing which induces chromothripsis that can lead to carcinogenesis in a single event.

KL-4

Applying an Integrative Approach for Risk Assessment on The Effects of Chemical Mixtures in The Context of Real-Life Risk Simulation.

Academician Aristides M. Tsatsakis

University of Crete, Greece

Biography

Professor, Academician Aristidis Tsatsakis, PhD, ERT, DSc, FATS, DHonC, DHonC, DHonC, HonProf, FMRAS, FMWAS, is the Director of the Department of Toxicology and Forensic Sciences of the Medical

School at the University of Crete. Prof. Tsatsakis has published well over 1000 articles, over 600 of them in ISI journals with more than 20,000 citations and on h-index 68. Prof. Tsatsakis has given over 200 keynote and plenary lectures in international congresses and has been the promoter and chair of numerous Symposiums and workshops in International Forum. Dr. Tsatsakis studies and concept on RLRS (real-life risks simulation) based on low dose combined long term exposures related to health issues, is a crucial element and the central driving force for application of theory to practice the safety evaluations in 21st century. Among many honorary titles: member of National Academy of Sciences of Russia and EUROTOX president (2014-2016). In December 2020, Prof. Tsatsakis was recognized as Highly Cited Researcher in the field of Pharmacology-Toxicology.

KL-4

Applying an Integrative Approach for Risk Assessment on The Effects of Chemical Mixtures in The Context of Real-Life Risk Simulation.

Dr. Elisavet Renieri

University of Crete, Greece

Biography

Dr. Elisavet Renieri (female), has a background in Biology (Department of Biology of the National and Kapodistrian University of Athens) and holds a PhD in Toxicology (2019) related to human health risk assessment for cumulative exposure to chemicals, which took place in the Centre of Toxicology Science & Research (CTSAR), Faculty of Medicine of the University of Crete. She is a researcher in CTSAR in the field of mixtures risk assessment and has an additional scientific interest in the development and optimization of telomere length assessment as a phenotypic biomarker of effect for long term exposures. Since early 2020 she is also a post-doctoral researcher in the HERACLES Research Center, involved with the development of systemic biology models with the use of omics. She is a European Registered Toxicologist (ERT) and a member of the Hellenic Society of toxicology.

Abstract

Real life risk simulation is often neglected in regulatory risk assessment. The paradigm shift of modern toxicology aims to assess real life exposures, paying particular attention to exposures to low doses, combined and long-term exposures when considering associations to health impacts. Within this context, two

new approaches have been proposed for the risk characterization of single chemicals and chemical mixtures: The source related Hazard Quotient (HQ_S) and Hazard Index (HIS) and the adversity specific Hazard Index (HI_A). In order to account for the aggregated exposure, the Source Related HQ approach was developed (HQ_S) where HQ_S is the ratio of the exposure from the specific source of interest to the respected reference values. The HQ_S, before being compared to the reference dose, are adjusted by a correction factor, in order to simulate aggregated exposure. A correction factor is calculated based on the permitted exposure contribution from the specific source to the permitted aggregated exposure. Additionally, in order to overcome limitations related to the classical HI approach where chemical specific ADIs that do not correspond to the same critical effect are used, an alternative approach of the HI_A is presented. The calculation of the HI_A is based on an analysis of the individual critical effects, in order to derive the critical effect and a risk characterization for the whole mixture. Case studies with the applied methodologies are also presented and critical overview of the current regulatory status is discussed.

KL-5

Effects of Circulating Small Extracellular Vesicle on Cancer Metastasis and Chemoresistance.

Prof. Keon Wook Kang

Seoul National University, Korea

Biography

Professor, Dr. Keon Wook Kang is the Director of BK21 education and research program of the College of Pharmacy, Seoul National University. In addition, Professor Kang served as the Vice Dean of the College of Pharmacy at Seoul National University (2017-2019) and the Vice Chair of the Admissions Headquater at Seoul National University (2020-2022). Dr. Kang obtained his bachelor's degree from the College of Pharmacy, Seoul National University, and his Master's and Ph.D. degrees from the same university in 1995 and 1999, respectively. After obtaining his doctorate, he worked as a postgraduate researcher at New Drug Development Research Center, SNU until 2001, and moved to University of California, Irvine as a postgraduate researcher and Research Associate until 2003. Dr. Kang published over 190 articles in SCI journals since becoming a faculty in 2003, and their SCOPUS H-index is 47. Dr. Kang's recent major research themes are the following two fields. The first is to identify the cell-cell interactions involved in the malignant process of cancer and external factors affecting it, and the second is to evaluate the relationship

between the genetic variation and disease progression in patients with chronic liver metabolic diseases. He is now the secretary-general of the Korean Society of Toxicology and Environmental Mutagenesis, and the chair of the scientific committee of the Korean Society of Pharmaceutical Sciences.

Abstract

Extracellular vesicles (EV) in the tumor microenvironment have emerged as crucial mediators that promote proliferation, metastasis, and chemoresistance. However, the role of circulating small EVs (csEV) in cancer progression remains poorly understood. In this study, we report that csEV facilitate cancer progression and determine its molecular mechanism. csEVs strongly promoted the migration of cancer cells via interaction with phosphatidylserine of csEVs. Among the three TAM receptors, TYRO3, AXL, and MerTK, TYRO3 mainly interacted with csEVs. csEV-mediated TYRO3 activation promoted migration and metastasis via the epithelial-mesenchymal transition and stimulation of RhoA in invasive cancer cells. Additionally, csEV-TYRO3 interaction induced YAP activation, which led to increased cell proliferation and chemoresistance. Combination treatment with gefitinib and KRCT-6j, a selective TYRO3 inhibitor, significantly reduced tumor volume in xenografts implanted with gefitinib-resistant non-small cell lung cancer cells. The results of this study show that TYRO3 activation by csEVs facilitates cancer cell migration and chemoresistance by activation of RhoA or YAP, indicating that the csEV/TYRO3 interaction may serve as a potential therapeutic target for aggressive cancers in the clinic. We further identified a potent and highly selective TYRO3 inhibitor, and explored the role of TYRO3 from the immuno-oncological point of view. Blockade of TYRO3 boosts anti-tumor immune responses in both the tumor-draining lymph nodes (TdLNs) and tumors in MC38-syngeneic mice models. Moreover, the combination of TYRO3 inhibitor and anti-PD-1 therapy exerts significant synergistic anti-tumor effects in anti-PD-1 non-responsive 4T1-syngeneic mice model. These findings demonstrate that csEVs are a novel driver in migration and survival of aggressive cancer cells via TYRO3 activation, and suggest potential usefulness of TYRO3 targeting strategy to handle aggressive cancer. This work was supported by supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (2021R1A2C2093196 (K.W. Kang)).

KL-6

Air Pollution Exposure Mitigation and Health Intervention: Insights from Source-Specific Cardiorespiratory Impairments.

Prof. Wei Huang

Peking University, China

Biography

Prof. Huang received her doctorate degree in Environmental Health at Harvard T.C. Chan School of Public Health in 2003, and then worked at the Health Effects Institute overseeing air pollution and health studies in Asia between 2003-2007. She joined Peking University in 2008, and now is a faculty member in the Department of Occupational and Environmental Health at Peking University of Public and serves as the Deputy Director of Peking University Institute of Environmental Medicine. Her research interests include air pollution exposure assessment, biological effects and risks of environmental exposures, and health intervention policy. She has served on multiple advisory panels and as working group members for the World Health Organization, International Agency for Research on Cancer, China Ministry of Ecology and Environment. She also serves as the co Editor-in-Chief for *International Journal of Hygiene and Environmental Health* (IJHEH), Associate Editor for *Science of the Total Environment* (STOTEN), and Editorial Board Member for *Environmental Epidemiology* in recent years. She is the Chair of Youth Committee of China Environmental Mutagen Society, and active Committee Members of International Society of Environmental Epidemiology (ISEE) and International Federation of Gynecology and Obstetrics (FIGO).

Abstract

In two longitudinal panels with repeated measurements, we observed that ambient air pollution significantly associated with cardiometabolic abnormalities in healthy adults and patients with chronic obstructive pulmonary disease (COPD). In healthy subjects, ambient particulates in small size fractions (particulate matter in diameter <2.5 μm [$PM_{2.5}$] and number concentrations of particles in sizes of 5 to 560 nm) and traffic-related pollutants (black carbon, nitrogen dioxide, and carbon monoxide) were observed in associations with abnormalities of cardiac repolarization and hemodynamics, as well as heightening responses of atherosclerotic vulnerable plaque, thrombogenicity, myocardial damage, and vascular and systemic

immune inflammation. In terms of metabolic health, air pollutant concentrations were closely related to worsening metrics of high-density lipoprotein functionality, proatherogenic lipoproteins, insulin resistance, and amino acid metabolism. For COPD patients, exposure to traffic-related air pollutants could prompt the genesis of large and small airway dysfunctions, along with elevation of cardiac injury, vascular calcific potential, airway/systemic inflammation and oxidative stress. Collectively, combustion-derived particulate organic matters, particularly originating from traffic emissions and coal burning, were significantly associated with adverse cardiorespiratory effects in both healthy and COPD subjects. Further, we conducted two systematic reviews funded by the WHO on the efficacy of short-term intervention at personal-level against air pollution. Results from the identified intervention studies showed that indoor portable air cleaner uses could contribute to some reductions in indoor PM concentrations, however, which remained well above WHO Global Air Quality Guideline Levels particularly in areas with high outdoor air pollution concentrations, and some beneficial changes were observed on cardiovascular health but with much limited evidence on respiratory health. In summary, our findings can serve as mechanistic demonstration linking potential detrimental cardiorespiratory effects of source-specific emissions, and provide insights on air pollution intervention priorities by calling for continuing efforts to reduce PM from combustion emissions.

KL-7

IARC Monographs on the Identification of Carcinogenic Hazards to Humans.

Dr. Federica Madia

The International Agency for Research on Cancer (IARC), France

Biography

Federica Madia, PhD, MS is a senior toxicologist within the Monographs programme of the Evidence Synthesis and Classification Branch of the International Agency for Research on Cancer (IARC). She is primarily supervising the mechanistic aspects of IARC Monographs, including the application of the key characteristics of carcinogens. Before she served as a scientific officer for nine years at the European Commission's Joint Research Centre (JRC). There, she contributed to the activities aimed at the development

of novel approaches to testing human systemic toxicity endpoints, in particular carcinogenicity and genotoxicity. In the previous 15 years, Federica was research scientist in Academia, working in various Institutions in US and Italy, at Leonard Davis School of Gerontology, University of Southern California (US), Mario Negri Sud, at the School of Pharmacy of University of Rome. Main area of research included biology of cancer and aging and age-related genomic instability plus further human toxicology and pharmacology research projects including mechanisms of flame retardants toxicity. She had also experience in the pharmaceuticals private sector and served as toxicology study director at CRO. Federica received a MS in Biology, a PhD in Pharmacology and Toxicology and Post-grad Certificate in Ecotoxicology from University of Rome Sapienza, Italy.

Abstract

The IARC Monographs Programme is an international, interdisciplinary approach to carcinogenic hazard identification operated by the International Agency for Research on Cancer (IARC), a specialized agency of the World Health Organization. Its overall objective is to identify preventable causes of cancer. Its principal product is the serial publication IARC Monographs on the Identification of Carcinogenic Hazards to Humans, which began in 1971 in accordance with a fundamental mission of the Agency: to prepare and distribute authoritative information on human cancer, its causes, and its prevention. The Monographs have evolved into what is considered as the World Health Organization's encyclopedia on the environmental and occupational causes of human cancer. Two or three volumes of the Monographs are prepared annually. From 1971 through June 2022, more than 1036 unique agents and exposures have been reviewed and evaluated in 132 meetings, each meeting resulting in a volume of the IARC Monographs. Agents may be re-evaluated as new information becomes available in the published scientific literature. The Monographs have proven to be useful worldwide to scientists, public health authorities and the public.

Here, the objective and scope of the IARC Monographs Programme, general principles and procedures to scientific review and evaluations are presented as reported in the amended Preamble to the IARC Monographs. This also includes a mention to the mechanistic discussion that has been restructured to more explicitly analyze evidence for the key characteristics of carcinogens identified during the Volume 100 Monographs and two subsequent expert workshops. In addition, a summary of the resulting evidence on the evaluation of cobalt, antimony compounds, and weapons-grade tungsten alloy from the recent Monograph vol 131 is reported.

KL-8

DNA Demethylation and Environmental Health Effects.

Prof. Hailin Wang

Chinese Academy of Sciences, China

Biography

Dr. Hailin Wang obtained his BSc in Chemistry from Wuhan University in 1991 and his PhD from the Dalian Institute of Chemical Physics, Chinese Academy of Sciences in 1997. He had done his post-doctoral research at the University of Alberta, Edmonton, Canada, and joined the Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences (Beijing) in December 2005, where he is Professor of Bioanalytical Chemistry and Toxicology. He developed advanced analytical technologies (UHPLC-MS/MS, qPCR, genome-wide sequencing) for characterization and functional study of DNA 5-methylcytosine and its oxidation intermediates and DNA N6-methyladenine. He for the first time showed the enhancement of genome-wide 5-hydroxymethylcytosine by nutrient vitamin C, revealing a role of vitamin C in the regulation of DNA modification, and his study established a direct linkage among vitamin C, Tet dioxygenases, and DNA methylation. As a world-wide seminal work, he discovered new epigenetic DNA modification (N6-methyladenine) in high eukaryotes (*Cell*, 2015). He also has his expertise in ultrasensitive analytical technologies (e.g., capillary electrophoresis-laser induced fluorescence polarization, single molecule fluorescence imaging, and UHPLC-MS/MS) for detection of carcinogenic DNA adducts and for study of DNA-repair proteins interactions. He published 250 peer-reviewed papers on leading journals, including *Cell, Nature, Science, Cell Research, Pro Natl Acad Sci USA, J Am Chem Soc, Cell Res, Cell Discovery, Nucleic Acids Res, EHP*. He is a member of the editorial advisory board in a number of scientific journals, e.g., *GPB, DNA repair, Chem Res Toxicol, J Chromatogr A, J Separation Sci*.

Abstract

DNA methylation at cytosine (5mC) as an important epigenetic marker regulates gene expression and renders cellular identity, and is critically involved in genome imprinting, inactivation of X chromosome and parasite elements, and documentation of epigenetic memory. DNA demethylation remarkably

contributes to the dynamics of 5mC in mammals and is critical for multiple biological processes, including animal cloning,nuclear reprogramming, development, and highly locus-specific regulation of gene activities. DNA demethylation can be initiated by the oxidation of 5mC and the formation of 5-hydroxymethylcytosine (5hmC), which are catalyzed by ten eleven translocation (Tet) family dioxygenases. The formed 5hmC can be diluted by DNA replication, suggesting a passive DNA demethylation pathway. Moreover, the 5hmC can be further oxidized by Tet proteins to form 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC), which can be excised by thymine DNA glycosylase (TDG) followed by the reintroduction of unmethylated cytosine through the base-excision repair (BER) pathway. This is an important pathway for active DNA demethylation. The radically altered methylation, as observed in replication-independent demethylation of the paternal genome in zygotes, may complete within hours. Genome-wide mapping analysis has shown a strong enrichment of 5hmC within exons and near transcription start sites (TSSs), pointing to a potential role in transcriptional regulation. Furthermore, impaired hydroxylation of 5mC has been observed in myelodysplastic syndromes, hepatocellular cancers and gliomas. We showed that a number environmental and nutrient molecules profoundly altered DNA demethylation, including vitamin C, redox-active quinones, heavy metals (e.g., nickel), pharmaceutics (e.g., anticancer anthracycline drugs), and environmental endocrine disruptors (e.g., BPA and BPS). The associated DNA demethylation mechanisms were also explored. For example, we identified a new feedback circuit of ERa activation–DNMT-TET2-DNA hydroxymethylation pathway in ER+ breast cancer cells and uncovered a pivotal role of TET2-mediated DNA hydroxymethylation in modulating BPA/BPS-stimulated proliferation. To our knowledge, we for the first time established a linkage among chemical exposure, DNA hydroxymethylation, and tumor-associated proliferation. These findings further clarify the estrogenic activity of BPA/BPS and its profound implications for the regulation of epigenetic DNA hydroxymethylation and cell proliferation.

Introduction of Invited Speakers (Symposia)

S1-1

DNA Adductomics in Human Tissues.

Prof. Haruhiko Sugimura

Hamamatsu University, Japan

Biography

After finishing medical school and obtaining license for medical doctor in1982, Faculty of Medicine, the University of Tokyo, Dr. Haruhiko Sugimura directly got in Graduate School, Faculty of Medicine, the University of Tokyo. His mentor was Dr. Wataru Mori (later he became the president of the University of Tokyo). He was trained as a pathologist on anatomical pathology and was awarded Doctor of Medical Science (Ph.D. equivalent) in 1986. His thesis was on acute or chronic liver disease. He became board certificated pathologists in 1987 and has been listed for 45 years. He spent post-doctoral training in Japan (1987, Research Resident, Epidemiology Division, National Cancer Center Research Institute, Tokyo) and USA (1988-1990, Molecular Epidemiology Section, Laboratory of Human Carcinogenesis, NCI, USA). In this period, he endeavored into the new discipline “molecular epidemiology of cancer” and work on genetic polymorphism, DNA adducts, and cancer susceptibility. After three years of training in NCI, he once came back as an Assistant Professor, Department of Pathology, the University of Tokyo, his alma mater, but soon was invited to the 1st Department of Pathology led by Prof. Isamu Kino, a distinguished GI tract pathologist as an Associate Professor, Hamamatsu University School of Medicine (1991). Since then he served as an Associate Professor (1991-1995), and Professor (1995-) of the same department (currently renamed as Department of Tumor Pathology). The original intention of the late Prof. Kino is introduction of molecular biology into pathology field, which Dr. Sugimura devoted himself with younger colleagues. He published 300 and more papers listed on PubMed and h-index is 78. He was awarded Japanese Pathology Award in 2015 and the topic is expounded in his review “Susceptibility to human cancer: From the perspective of a pathologist. (*Pathol Int*. 2016. PMID: 27216305)”. He has been an active member of AACR, JCA, and JSP for years. He served as a vice director of Hamamatsu University of School of Medicine and a director of the library of Hamamatsu University School of Medicine, 2020.4-2022.3. In May 2022 he was also appointed as the 11th director of Sasaki Institute Sasaki Foundation, Tokyo which used to be a leading

institute of carcinogenesis (Drs. Tomizo Yoshida and Takaoki Sasaki). He has trained many international students including Rwandan scientists.

Abstract

DNA modifications and adduct formations are thought to be essential incipience of mutations, ultimate origin of carcinogenesis. There have been many excellent systems of experimental carcinogenesis and mechanistic information on covalent bonding of chemical carcinogen to the base of DNA, DNA damage and repair, mispairing and mutation are available, from rodents to bacteria. The reality of human carcinogenesis in this context, however, is still scarce. We have not yet had the whole steps of environmental carcinogenesis especially existence of involvement of DNA adducts in human though the recent study of mutation signatures in tumors suggest specific mutation processes according to individual carcinogens. In this presentation I will address the challenge in adductome approach in human tissues.

S1-2

Discovery of Functional Link between DNA Double-strand Break Repair and the Early Transcriptional Response to the Sex Hormone.

Prof. Shunichi Takeda

Shenzhen University, China

Biography

Shunichi Takeda, M.D, Ph.D, is a Distinguished Professor of Shenzhen University School of Medicine, Emeritus professor of Kyoto University, and worked as the Department of Radiation Genetics at Kyoto University during 1998-2020. Dr. Shunichi Takeda has studied molecular mechanism of radiotherapy and chemotherapy of tumors by employing a reverse genetic approach using a chicken B lymphocyte line technique. Prof. Shunichi Takeda has published more than 270 SCI articles in high-profile journals such as *Nature*, *Cell*, *Immunity*, *EMBO J*, *Molecular Cell*, *PNAS*, *Cell Rep*, with more than 18,000 citations and single paper have been cited more than 1500 times, H index: 74. Prof. Takeda has been invited to given keynote lectures and oral presentations at more than 70 international conferences. Dr. Shunichi Takeda studies DNA damage response and tumorigenesis, based on constructed more than 100 gene knockout cell

lines. Among many honorary titles: International Senior Scientists, Outstanding Talent of Pearl River, Member of International Expert Committee of Shenzhen University. He also works as the editorial board member of *Nucleic Acids Research (NAR), Cancer and DNA Repair.*

Abstract

Sex hormones, androgen and estrogen, bind to their receptors (AR and ER) and control the expression of many target genes. Ligand-associated AR and ER bind to target genes as transcription factors at transcription regulatory sequences, including promoter and enhancer. Activated AR and ER strongly stimulate the proliferation of the epithelial cells in prostate and mammary glands, respectively. The transcriptional response to sex hormones is achieved by the activation of topoisomerase II (TOP2) catalysis at promoters and enhancers. TOP2 catalyzes strand passage reactions, which involve the movement of one intact double-stranded DNA duplex through a transient enzyme-bridged break in another (gated helix). TOP2 covalently bind to the 5' end of this transient break and rejoin it through the intrinsic ligation activity of TOP2. TOP2 often fails to rejoin, and resulting DNA double-strand breaks (DSBs) are called stalled TOP2 cleavage complexes (TOP2ccs). Stalled TOP2ccs are rejoined by the removal of 5' TOP2 adducts followed by ligation by nonhomologous end-joining (NHEJ). The removal of TOP2 adducts is achieved by a few parallel pathways involving ataxia telangiectasia mutated (ATM), tyrosyl DNA phosphodiesterase-2 (TDP2), and Breast cancer susceptibility gene I (BRCA1).We revealed that physiological concentrations of androgen and estrogen generate DSBs in breast and prostate epithelial cells when they are deficient in either ATM, TDP2, or NHEJ. The DSB formation depends on functional AR and ER and requires TOP2. The loss of ATM, TDP2, and NHEJ changes early transcriptional response to androgen and estrogen. The data uncovered the previously unknown link between DSB repair and early transcriptional response. Remarkably, a defect in ATM, TDP2, or NHEJ causes the overexpression of c-MYC oncogene in response to androgen and estrogen in mice. We propose that the sex hormone induces TOP2-dependent DSBs at transcription regulatory sequences and a defect in DSB repair increases the risk of breast and prostate carcinogenesis.

S1-3

Paternal Environmental Stress: From Sperm Epigenome to Offspring Synapse Organization.

Prof. Yankai Xia

Nanjing Medical University, China

Biography

Prof. Yankai Xia is the vice president of Nanjing Medical University and professor of Toxicology at School of Public Health. He is the Deputy Director of International Joint Research Center for Environment and Human Health, China and the PI of State Key Laboratory of Reproductive Medicine and Key Laboratory of Modern Toxicology. He works on environmental exposure and reproductive health. He has published >280 peer-reviewed research articles. He has received numerous academic awards, including the Second Prize of National S&T Progress Award. He was elected fellow of the International Society of Exposure Science (ISES), Birth Cohort Consortium of Asia (BiCCA) and several Chinese academic committees. Prof. Xia also acts as Associate Editor/Editor of several distinguished journals in the environmental field.

Abstract

Recently, paternal environmental stress has received increasing concern due to its potential adverse effects on offspring health. However, the underlying mechanism remains elusive. Sperm acts as a critical memory carrier that records paternal environmental stress through epigenetic changes such as DNA methylation, histone modifications, and non-coding RNAs, thus resulting in heritable changes in gene expression. Among various paternal environmental stresses, we focused on Glufosinate-ammonium (GLA), a widely used herbicide with emerging concern over its reproductive toxicity. In our study, adult male C57BL/6J mice were administered 0.2 mg/kg·day GLA for 5 weeks, and then copulated with female DBA/2 mice to obtain offspring. Neurobehavioral tests showed that paternal GLA exposure induced behavioral abnormalities including decreased social novelty, learning and memory in 5-week-old offspring. To uncover memory transmission from father to offspring, we focused on epigenetic changes carried by sperm. After examination on fertility, testis histology and semen quality in the GLA group, we performed deep sequencing to identify DNA methylation, transcriptionally active (H3K4me3 and H3K27ac) and repressive (H3K27me3

and H3K9me3) histone modifications, and mRNA transcript levels in sperm. We found no significant abnormality either on fertility, testis histology or semen quality-related indicators in GLA mice. Next generation sequencing showed alterations of these epigenetic marks and extensive transcription inhibition in sperm. Differential active marks were enriched at promoters and putative enhancers, while repressive marks were mainly distributed at intergenic regions and introns. They were mainly enriched in pathways related to synapse organization. When we zoomed in these regions, increased H3K4me3 overlaps H3K27ac loci at the gene promoter of Phkg2, which was actively expressed in GLA sperm. Moreover, histology analysis showed that paternal GLA exposure decreased dendrite complexity and spine density in hippocampus and prefrontal cortex of 5-week- old offspring, indicating abnormal synapse organization. These results suggested that GLA predominantly affected sperm epigenome and transcriptome, with little effect on fertility, testis histology or semen quality. These changes in sperm epigenetic marks induced by paternal GLA exposure might lead to the synapse organization abnormalities in hippocampus, thus explaining decreased memory in offspring. Further studies are still required to better understand the information in sperm epigenome under paternal environmental stress, and its impact on offspring health.

S1-4

The Emerging Role of Nfe2l1 in Carcinogenesis: Action as and Beyond a Transcription Factor.

Prof. Yuanyuan Xu

China Medical University, China

Biography

Dr. Yuanyuan Xu received the PhD degree in China Medical University and did Postdoc research in National Institute of Environmental Health Sciences, USA. Her research mainly focuses on mechanisms underlying chemical carcinogenesis. She has over 60 publications in peer-reviewed academic journals, such as *Environ Health Perspect*, *Redox Biol* and *Free Radic Biol Med*, and serves in editorial board of *Toxicol Appl Pharmacol* and *Regul Toxicol Pharmacol*. Her research work won 7 awards for young scientist from the Society of Toxicology, USA and International Union of Toxicology. She is the Principal Investigator of three grants form National Science Foundation of China, and has been selected as the Pandeng Scholar and Outstanding Young Scientist in Revitalization Talents Program in Liaoning Province.

Abstract

Nuclear factor erythroid-2-related factor 1 (NFE2L1) is a well-known cap'n'collar protein family member that plays critical roles in regulating a wide range of essential cellular functions. This factor has also been implicated in the pathogenesis of cancer development. Our previous studies have reported NFE2L1 acts as a transcription factor in oxidative stress defense, inflammation, metabolism, and differentiation. In a recent study, we investigated the role of Nfe2l1 in chemical carcinogenesis by using alveolar type II epithelial (ATII) cell-specific *Nfe2l1* knockout (*Nfe2l1* (ATII)-KO) mice treated with the lung adenocarcinoma inducer urethane (Ure). Under basal conditions, *Nfe2l1* (ATII)-KO mice showed no significant alteration in the lung functions and tissue histology, while *Nfe2l1* (ATII)-KO mice, both male and female, showed exacerbated lung tumor formation after Ure treatment. Immunochemical analysis found that the tumor was SPC, a ATII cell marker, positive. KEGG pathway enrichment analysis of differential expressing genes in separated ATII cells from the 7-week Ure-exposed lungs disclosed that cell cycle and DNA replication are the top two pathways affected by *Nfe2l1* knockout. Since Ure is a classic DNA mutagen, we tested DNA damage in the lung after acute Ure exposure. More γH2AX-staining cells were observed in *Nfe2l1* (ATII)-KO mice. In line with the in vivo observation, different cell lines with *Nfe2l1* knockdown showed server DNA damage caused by chemical or physical DNA insults. ROS scavenger only partially rescued DNA damage resulting from *Nfe2l1* deficiency. Interestingly, PARP1, a key enzyme in DNA damage repair, was suppressed in protein levels and activity in *Nfe2l1*-silenced cells in response to DNA damage. mRNA levels of PARP1 were not significantly affected following knockdown of *Nfe2l1*, ruling out the possibility that *Nfe2l1* transcriptionally regulates PARP1 expression. However, PARP1 protein stability was reduced by *Nfe2l1* silencing, which could be reversed by the proteasome inhibitors. Then, we subjected PARP1-GFP MLE12 cells to UV laser-microirradiation to detect the effect of *Nfe2l1* silencing on PARP1 response. *Nfe2l1* silencing markedly inhibited PARP1 localization at the DNA damage stripes even when PARP1 were overexpressed. HADDOCK2.4 molecular docking prediction suggests the possible interaction of these two proteins. Nuclear translocation of NFE2L1 was synchronized with increase in PARP1 protein after DNA damage. Co-localization of NFE2L1 and PARP1 in response to DNA damage was observed by immunofluorescence. Immunoprecipitation and immunoblotting analyses found the interaction the two proteins, which could not be abrogated by ethidium bromide. Post-translational modification of PARP1 modulates stability and activity of this protein. *Nfe2l1* silencing was found to increase the ubiquitination levels of endogenous PARP1 in response to DNA damage. Of note, the lower protein levels of NFE2L1 in human lung adenocarcinoma were found as compared to non-tumor adjunct tissue. Collectively, these findings suggest that NFE2l1 may act as a tumor suppressor and uncover a previously unrecognized mechanistic link between NFE2L1 and PARP1 in the regulation of cellular response to DNA damage.

S1-5

Enhanced Gastric Tumorigenesis by Accumulation of Tumor-Associated Macrophage in the Absence of Histamine Signal.

Prof. Ki Taek Nam

Yonsei University, Korea

Biography

Professor, Ki Taek Nam, D.V.M., PhD, AGAF, DKCLAM is Tenured Full Professor, Severance Biomedical Science Institute and the Director of the Dep. Of Laboratory Animal Resource, Yonsei Biomedical Research Institute, Yonsei University College of Medicine. Prof. Nam has published well over 100 articles as main authors including high impact journal such as *J Am Chem Soc* (2019), *ACS Nano* (2018, 2019), *Biomaterials* (2017,2022), *Angew Chem* (2022), *NPJ Precis Oncol* (2022), *Biosens Bioelectron* (2022), *Cancer Lett* (2020), *Gastroenterology* (2007, 2009, 2010, 2021), *Gut* (2004, 2012, 2022). Prof. Nam has given over 70 keynote and plenary lectures in international congresses and has been the promoter and chair of numerous Symposiums and workshops in International Forum. Dr. Nam was trained as a Veterinarian with special qualifications Veterinary Pathology and mouse pathology at Seoul National University. He has broad research training in epithelial cancer biology and his studies focused on the induction of gastric cancer in rodent models. He has focused his research efforts on understanding mouse models for the origin of metaplasia in the stomach and the mechanisms leading to induction of colon cancer. Among many honorary titles: member of AMMRA (Asian Mutant Mouse Resource Association) publication committee and vice president of KOREA Mouse Phenotyping Center. Prof. Nam was recognized as Highly Cited Researcher in the field of Gasteroenterology–Tissues Stem cell- Toxicopathology.

Abstract

Histamine in the stomach is traditionally considered to regulate acid secretion but has also been reported to participate in macrophage differentiation, which plays an important role in tissue homeostasis. Therefore, this study aimed to uncover the precise role of histamine in mediating macrophage differentiation and in maintaining stomach homeostasis. Here, we expand on this role using histidine decarboxylase knockout ($Hdc^{-/-}$) mice with hypertrophic gastropathy. In-depth in vivo studies were performed in $Hdc^{-/-}$ mice, germ-free $Hdc^{-/-}$ mice and bone-marrow transplanted $Hdc^{-/-}$ mice. The stomach macrophage populations and

function were characterized by flow cytometry. To identify stomach macrophages and find the new macrophage population, we performed single-cell RNA seq analysis on $Hdc^{+/+}$ and $Hdc^{-/-}$ stomach tissues. Single-cell RNA-sequencing and flow cytometry of the stomach cells of $Hdc^{-/-}$ mice revealed alterations in the ratios of three distinct tissue macrophage populations ($F4/80^{+}Il1b^{high}$, $F4/80^{+}CD93^{+}$, and $F4/80^{-}MHCI-I^{high}CD74^{high}$). Tissue macrophages of the stomach of $Hdc^{-/-}$ mice showed impaired phagocytic activity, increasing the bacterial burden of the stomach and attenuating hypertrophic gastropathy in germ-free $Hdc^{-/-}$ mice. The transplantation of bone marrow cells of $Hdc^{+/+}$ mice to $Hdc^{-/-}$ mice recovered the normal differentiation of stomach macrophages and relieved the hypertrophic gastropathy of $Hdc^{-/-}$ mice. This study demonstrated the importance of histamine signaling in tissue macrophage differentiation and maintenance of gastric homeostasis through the suppression of bacterial overgrowth in the stomach.

S1-6

Maternal Cadmium Exposure During Gestation Impairs Hippocampal Neurogenesis and Cognition via Reducing Placenta-Derived Estrogen in Offspring.

Prof. Hua Wang

Anhui Medical University, China

Biography

Prof. Hua Wang has long engaged in early-life exposure to environmental metals and adverse offspring outcomes. He is a member of Asian Alliance for Arsenic and Health, Chinese Pharmacological Society, Chinese Society of Toxicology, Chinese Environmental Mutagen Society. He is also a standing member of Youth Committee and Epigenetic Toxicology Professional Committee of Chinese Society of Toxicology, Professional Committees of Teratogenesis and Environmental stress and Health Damage in Chinese Environmental Mutagen Society, a Chairman of Health Toxicology Professional Committee of Anhui Preventive Medical Association, and a standing council of Anhui Provincial Environmental Mutagen Society. He is also a peer reviewer in *Redox Biology, Journal of Hazardous Materials, Environment International, Science of the total Environment, Ecotoxicology and Environmental Safety, Toxicological Sciences, Journal of Endocrinology, Toxicology, etc*.

Abstract

Early-life exposure to environmental cadmium (Cd) is known to cause developmental disorders, yet the effect and mechanism of gestational exposure to Cd on the offspring's cognitive function remains unclear. Placenta as a well-established target organ for Cd-impaired fetal development, its role in estrogen regulation and offspring cognitive function is unknown. Our in vivo experiments found that gestational Cd exposure impaired cognitive function in adult male offspring, accompanied with lowered 17β-estradiol (E2) levels in the male fetal brain upon Cd exposure. Correspondingly, the expression of synapse-associated proteins including brain-derived neurotrophic factor (BDNF), post-synaptic density protein 95 (PSD95) and synapsin-1 were downregulated, which were reversed when supplemented with E2 hormone during gestation. Further observation showed placental estrogen synthesis inhibition and general control non-derepressible 2 (GCN2) signaling activation upon Cd exposure, whereas placental estrogen synthesis could be restored through inhibiting GCN2 activity. Based on ovariectomy (OVX) of pregnant mice, we confirmed that Cd exposure reduced E2 level in fetal brain via inhibited placental-derived estrogen synthesis. The aforementioned Cd-induced fetal brain injury and cognitive impairment in adult offspring were significantly alleviated when pregnant dams were supplemented with anti-stress agent N-Acetyl-L-cysteine. In summary, Cd disrupted placental-derived estrogen synthesis via activating GCN2 signaling, and thereby caused cognitive impairment in adult offspring mice. Our findings suggest that placental-derived estrogen may be an effect marker of environmental toxicants-evoked cognitive dysfunction in adult offspring, and suggest that environmental toxicants may affect the fetal brain development via placenta-fetal-brain axis.

S1-7

The Cardiovascular Toxicity of Aryl Organophosphate Flame Retardants in Embryonic Development.

Prof. Yanhong Wei

Sun Yat-sen University, China

Biography

Dr. Wei is a professor of Toxicology at the Sun Yat-sen University. She is dedicated to studying the adverse health effects of environmental chemicals on the cardiovascular system and development. She received her

doctorate in Ecotoxicology from Chinese Academy of Sciences in 2008 and was a postdoctoral fellow at the Johns Hopkins University from 2008 to 2016. Dr. Wei is the vice-chair of the Committee of Biochemistry and Molecular Toxicology in Chinese Society of Toxicology and the vice-chair of the Youth Committee of Chinese Environmental Mutagen Society. She is currently an officer in the Cardiovascular Toxicology Specialty Section of the Society of Toxicology. She published 27 peer-reviewed articles in SCI-indexed journals, including PNAS. She acts as a principal investigator in three general programs supported by the National Natural Science Foundation of China. She serves in the editorial boards of the *Environmental Pollution* and the *Archives of Toxicology*.

Abstract

As brominated flame retardants are regulated and phased out worldwide, organophosphorus flame retardants (OPFRs) are becoming a popular alternative. As such, OPFRs' hazardous effects on the environment are becoming a growing concern. The increasing production and application of aryl organophosphate flame retardants (Aryl-OPFRs), the typical non-halogenated flame retardants, give rise to the severe and worsening environmental impacts. Cardiovascular system is the main target of Aryl-OPFRs, which exerts the stronger cardiovascular toxicity than alkyl organophosphate flame retardants in zebrafish. Cardiovascular system, especially blood vessels which consist of arteries, veins, and capillaries, is highly heterogenous. Exposure to xenobiotics leads to distinct cellular responses and regulatory fashions in various types of blood vessels in all kinds of tissues. However, the characteristics of the adverse effects on the cardiovascular system and the underlying mechanisms by Aryl-OPFRs exposure are poorly understood. Here, we develop a deep learning-based quantitative framework to characterize vascular profiles in Tg (fli1a:eGFP) zebrafish larvae by exploiting high-resolution fluorescence images from high-content screening. Using the framework, we analyzed morphological features of whole trunk blood vessels as well as the cerebral vasculature and quantitated vascular disruptions caused by Aryl-OPFRs, Alkyl-OPFRs, BFRs, and the emerging FRs. The results showed that chemical insults led to heterogeneous cardiovascular patterns manifested by 34 architecture indices, and the common cardinal vein was the most affected vessel. In the quantification of vascular lesions, tert-butylphenyl diphenyl phosphate scored highest in Aryl-OPFRs. The average score of Aryl-OPFRs was higher than that of Alkyl-OPFRs. We selected BDP for further investigation of intergenerational toxicity in cardiovascular development. The results showed that parental exposure to 30 ng/L to 30 μg/L BDP led to vascular disruptions in the offsprings. This study extends our knowledge of OPFR's cardiovascular toxicity. More importantly, the findings will contribute to the identification of early responses, characterization of toxicity and the health risk assessment of Aryl-OPFR.

S1-8

Injury Target, Toxic Effect and Molecular Mechanism of Atmospheric Pollutants from Coal-Burning Area.

Prof. Nan Sang

Shanxi University, China

Biography

Sang Nan, professor, now works in Research Center of Environment and Health, College of Environmental and Resource, Shanxi University. She is the winner of National Natural Science Foundation-Outstanding Youth Foundation, and also received a number of awards, including Baogang excellent teacher award and Huo Yingdong young teacher award. She has been engaged in environmental toxicology and environmental health for a long time, especially focusing on the toxicology and health effects of air pollution. She has more than 100 papers have been published in international journals in the field of environmental toxicology and environmental health, including *Environmental Health Perspectives*, *Environmental Science & Technology*, *Toxicological Sciences*, etc. She acts as associated editor of Journal of *Hazardous Materials* and editorial board member of *Science of The Total Environment*.

Abstract

Our country is experiencing complex atmospheric pollution, and there are many challenges in clarifying the health risk of atmospheric pollution, especially discriminating toxic component, revealing effect and molecular mechanism, and finding offspring outcome. Focusing on “injury target, toxic effect and molecular mechanism of main atmospheric pollutants”, we conducted long and systematic studies and obtained the following innovative results. 1) SO_2 inhalation caused heart injury through free radical accumulation, mitochondrial dysfunction and lipid metabolism perturbation, the damage different from that of traditional respiratory system. 2) Maternal NO_2 exposure reduced the methylation level of interleukin-4 (Il4) gene, promoted the imbalance of immune factors Th1/Th2 differentiation in offspring, the novel mechanism for cardiopulmonary injury in early life and disease susceptibility change in later life. 3) $PM_{2.5}$ exposure stimulated neuroinflammation, down-regulated miR-574-5p expression and elevated β-secretase 1 activity, the new pathway for resulting in neurodegenerative diseases. 4) The inorganic sulfate in particulate matter regulated E-cadherin level by affecting methylation level, and then led to epithelial-to- mesenchymal transition and finally promoted the progression of lung cancer. Our findings provided scientific support for toxic identification, risk management and prevention and therapy of atmospheric pollutants.

S2-1

QSAR Prediction of Ames Mutagenicity.

Dr. Kiyohiro Hashimoto

Takeda Pharmaceutical, Japan

Biography

Kiyohiro Hashimoto, PhD, is an associate scientific fellow at Takeda Pharmaceutical Co. Ltd, serving as a SME for genetic toxicology, safety assessment and qualification of impurity. He belongs to the Japanese Environmental Mutagen and Genome Society (JEMS), for which he is serving as BOD for international relationship matters. He also belongs to the Japanese Pharmaceutical Manufacturing Association, leading the task force team as an expert of ICHM7 EWG member. He has been involved in this genetic toxicology research area more than 20 years, and during this period he has stayed at University of North Carolina Chapel hill as a visiting scholar, supervised by Prof. Jim Swenberg. Main area of research included biology of genotoxicity testing for drug discovery, mechanism investigation of genotoxic compounds, and regulatory science related toxicology research.

Abstract

QSAR has shown remarkable progress since the beginning of the 21st century. In particular, it has been widely used in industry-government-academia research institutes as a prediction tool for Ames test, and its recognition has remarkably improved. The ICHM7 guideline enacted in 2014 is considered to have caused this phenomenon. Following the establishment of the guideline, pharmaceutical companies became obligated to use QSARs to predict mutagenicity of impurities in pharmaceutical products, and based on the results, they were required to submit the control of impurities to the regulatory authorities. Therefore, authorities were also required to use QSAR, and the number of users spread drastically. In addition, the prediction accuracy has been improving as the number of users increases. This is likely due to a positive cycle where QSAR vendors continued to make efforts to incorporate a wider range of data and users provided data to improve accuracy. For example, over 10,000 compounds were provided in the QSAR challenge program and captured in the database, resulting in improved prediction accuracy. To provide the speakers' personal opinions on how the QSAR prediction accuracy will be improved, what factors have hindered the improvement in accuracy, and whether the "QSAR prediction" will be accepted as an alternative to the existing Ames test in the future.

S2-2

A Toxicity Pathway-Based Approach to Develop Adverse Outcome Pathway.

Prof. Dianke Yu

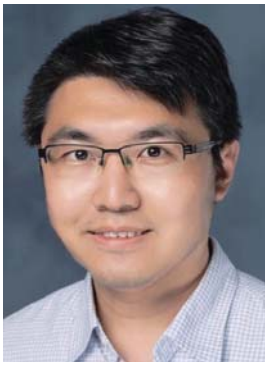
Qingdao University, China

Biography

Dianke Yu, Professor, School of Public Health, Qingdao University. Professor Yu received his Ph.D. degree from Chinese Academy of Medical Science (CAMS), China. After working at National Center for Toxicological Research (NCTR) for four years (2013-2017), he joined the school of public health in Qingdao University. He now serves as the Vice Dean of School of Public health since 2021. His main research interests are in molecular toxicology and systems toxicology, especially in the identification, epigenetic modulation, and quantitative analysis of key toxicity pathways in response to environmental chemicals. His research is supported by multiple fundings received from the National Key Research and Development Program of China, National Natural Science Foundation of China, and Thousand Young Talents Recruitment Programe. He has published 120+ articles in well-respected SCI journals, including *Nat Genet*, *Environ Int*, *J Hazard Mater*, *Arch Toxicol*, and *Environ Pollut*.

Abstract

With numerous new chemicals introduced into the environment every day, identification of their potential hazards to the environment and human health is a considerable challenge. Toxicity pathway is an essentially physiological pathway that could function and maintain homeostasis, and once sufficiently perturbed to the degree beyond adaptation, become toxicity pathway. Adverse outcome pathway (AOP), which sequentially starts from a molecular initiating event, triggers multiple key events in cells or organs, and eventually results in an adverse outcome, is a promising tool to help achieve this goal as it can bring in vitro testing into toxicity measurement and understanding. Here, we proposed a new approach to construct AOP based on toxicity pathways, by integrating the omics data and systems biology understanding, which supplies new clues to the identification of potential hazards and risk assessment of environmental chemicals.



S2-3

Development of Physiologically Based Pharmacokinetic (PBPK) Models Within Bayesian Framework for Perfluorooctane Sulfonate (PFOS) and Its Implications in the Derivation of Health-Based Toxicity Values.

Research Assistant Prof. Wei-Chun Chou

University of Florida, United States

Biography

Dr. Wei-Chun Chou graduated from the Department of Biomedical Engineering and Environmental Sciences at National Tsing Hua University and is currently working as a research assistant professor at the Department of Environmental and Global Health and the Center for Environmental and Human Toxicology at the University of Florida. Dr. Chou's research is to develop a computational model based on Bioinformatics, Computational toxicology, and artificial intelligence to study the research questions about environmental health and human health risk assessment. In 2019, he was awarded the Anderson & Clewell Trainee Award and the Outstanding Postdoctoral Research Award from the Society of Toxicology (SOT). His paper also was awarded the best paper award by the Biological Modeling and risk assessment Specialty Section of the SOT in 2020 and 2022. Dr. Chou participated in several NIH and USDA projects, including (1) NIH/NIBB R03 Grant: Physiologically based pharmacokinetic modeling and analysis of administration route-dependent tissue distribution of gold nanoparticles; (2) USDA/NIFA Award: Food Animal Residue Avoidance Databank (FARAD); (3) NIH/NIBB R01 Grant: Development of a web-based predictive model of nanoparticle delivery to tumors by integrating physiologically-based pharmacokinetic modeling with artificial intelligence. He is currently a guest editor of Toxics and an invited reviewer for several well-known international journals, such as *Computation Toxicology, Environmental Health Perspectives, Journal of Hazardous and Materials,* and *Environment International*.

Abstract

Inter- and intra-species variability in chemical pharmacokinetics and toxicological endpoints results in a significant difference in the estimation of reference dose (RfD), thus leading to an enormous challenge in human health risk assessments. Therefore, it is important to address an integrated framework with new approach methods (NAMs) to characterize variability and susceptibility. Recently, we developed an integrated framework by combing Bayesian statics with physiologically based pharmacokinetic (PBPK)

models to characterize uncertainty and variability between species, individuals, and life stages. This Bayesian population PBPK model has been used in the estimation of RfD from interspecies extrapolations, simulation of the internal dose metrics for potentially sensitive subpopulations, and prediction of in vitro to in vivo extrapolation (IVIVE) of kinetic and toxicity data. In this presentation, I will introduce how we develop mechanistic PBPK model structure in different species, chemicals, and life stages within the Bayesian hierarchical framework and application for a case study with Perfluorooctane Sulfonate (PFOS) risk assessments.

S2-4

Analytical Development for Environmental Exposome Research.

Prof. Da Chen

Jinan University, China

Biography

Prof. Da Chen is a Professor and Associate Dean at the School of Environment, Jinan University. He received his Ph.D. at The College of William and Mary in 2009 and doctoral training at the National Wildlife Research Centre, Environmental and Climate Change Canada. He had worked as an Assistant Professor at the Southern Illinois University Carbondale. Chen's research has focused on the development of exposome-based analytical platform, exploration of the environmental distributions and fate of chemicals of emerging concern (CECs), and characterization of human exposure to CECs and subsequent health risks. In particular, his research focuses on gestational exposure to CECs and aims to study the links between environmental exposure and adverse pregnancy outcomes from an exposome perspective. He has published more than 150 scientific papers and received awards such as National Environmental Protection Technology Award and Guangdong Science and Technology Award. Prof. Chen is currently an Associate Editor of *Environment International* and *Environmental Pollution*, and an editorial board member of *Environmental Science & Technology Letters*. He is also a committee member of Environmental Science Society of China and Chinese Environmental Mutagen Society.

Abstract

Over the past decade, “exposome” has emerged as a novel research paradigm in many fields including epidemiology, biotechnology, clinical research, and other environmental health sciences. The concept of “human exposome” encompasses the totality of a person’s environmental exposures from conception onwards, which complements the genome. The concept has driven the integration of both internal and external factors into the study of adverse health outcomes in humans in order to achieve a comprehensive assessment of the causes and mechanisms associated with health outcomes. However, although the exposome concept is fascinating, the approach to “exposome” is very complicated and challenging. One of the major challenges is to determine numerous exogenous and endogenous molecules in biological specimens in order to characterize both external and internal chemical exposure. The numerous environmental chemicals complicate analytical characterization in human blood or urine. Complex environmental and biological transformation also make the identification of exposure biomarkers extremely difficult. Exposure markers also dynamically change along with age, gender, population, and territories, requiring accurate monitoring. In response to the analytical challenges during exposome applications, we developed an integrated analytical platform to determine both exogenous and endogenous molecules in biological specimens. The framework combines target, suspect screening, and non-target techniques based advanced mass spectrometry and databases. Target analysis can achieve high-throughput determination of over 600 environmental chemicals in blood and urine with small volumes. Suspect screening aims to determine chemicals structurally similar to known molecules and enhance the detection sensitivities via sample treatment and mass spectral optimization. Non-target screening aims to capture mass spectral signals in order to screen for possible chemicals in the samples with high-resolution mass spectrometer. The combined framework is expected to largely facilitate the application of exposome science in human health research.

S2-5

Metabolic Mechanisms and Toxic Effects of Polycyclic Aromatic Hydrocarbons Regulated by CYP Enzymes Under Combined Pollution.

Associate Prof. Kai Luo

Southeast University, China

Biography

Dr. Kai Luo is now an associate professor in Key Laboratory of Environmental Medicine Engineering, Ministry of Education, School of Public Health, Southeast University. Dr. Luo obtained his doctorate in Geography (Environmental Geography) from Peking University and then worked as a postdoctoral associate at Masonic Cancer Center, the University of Minnesota. Dr. Luo's laboratory is focused on understanding the ways carcinogens in tobacco and the environment cause cancer. To do this he and his group study the mechanisms by which these compounds enter the human body, are metabolized, and ultimately bind to DNA, causing mutations that result in cancer. Dr Luo's research team has developed methods to analyze human urine for these compounds, their metabolites and the DNA damage caused by the carcinogens.

Abstract

Benzo[a]pyrene (BaP) is a well-studied pro-carcinogen that is metabolically activated by cytochrome P450 enzymes. Cytochrome P450 especially CYP1 has been considered to play a central role in the metabolism of BaP, which is essential for the formation of DNA adducts or the detoxification metabolism. While previous studies got diverse results on the effect of induction of CYP1 on BaP-DNA adduct formation. We gave oral doses of deuterated phenanthrene ([D_{10}]Phe), a non-carcinogenic surrogate of carcinogenic PAH such as benzo[a]pyrene, to smokers (N = 170, 1 or 10 μg doses) and non-smokers (N = 57, 1 μg dose). Bioactivation products (dihydrodiol and tetraol) and detoxification products (phenols) of [D_{10}]Phe were determined in 6-h urine to obtain a comprehensive metabolic profile. Cigarette smoking increased the bioactivation of [D_{10}]Phe and decreased its detoxification resulting in significantly different metabolic patterns between smokers and non-smokers ($P < 0.01$), consistent with increased cancer risk in smokers. The Phe bioactivation ratios ([D_{10}]PheT/total [D_9]OHPhe) were significantly higher (2.3 ($P < 0.01$) to 4.8 ($P < 0.001$) fold) in smokers than non-smokers. With solid human in vivo evidence, our results for the first time demonstrate that induction of CYP1 enzymes by cigarette smoking enhances the metabolic activation of Phe, structurally representative of carcinogenic PAH BaP, in humans, strongly supporting their causal role in cancers caused by smoking.

S2-6

Applying Multi-Omics Approach to Reveal the Lung Cancer Biomarker.

Associate Prof. Ting Xiao

Chinese Academy of Medical Sciences and Peking Union Medical College, China

Biography

Ting Xiao graduated from Peking Union Medical College in 2005 with a doctor's degree in Oncology. Since 2005, as an associate researcher, and a master's supervisor she has worked in the State Key Laboratory of molecular oncology, the Cancer Hospital of the Chinese Academy of Medical Sciences. The research direction is the molecular mechanism and molecular markers of the occurrence and development of malignant tumors. By using multi omics, and the molecular markers for early diagnosis, efficacy evaluation and prognosis judgment of tumors are explored to develop their clinical application value. Has successively presided over the National Natural Science Foundation of China, the Beijing Natural Science Foundation and other projects, and participated in the 973 program, the 863 program, the national key R & D program.

Abstract

Objective: In China, the incidence rate and mortality of lung cancer have ranked first among all malignant tumors. Lung adenocarcinoma is the most common pathological type in non-small cell lung cancer, accounting for about 50% of the incidence rate of non-small cell lung cancer. Compared with other pathological subtypes of lung cancer, the proportion of non-smoking lung adenocarcinoma population is significantly higher, indicating the complexity of its pathogenesis. The purpose of this study is to identify differential proteins that are significantly related to the occurrence, development and prognosis of lung adenocarcinoma by integrating proteomics and phosphorylation proteomics based on large-scale clinical data, and to search for tumor markers of lung adenocarcinoma.

Methods: a total of 103 primary tumor tissues of lung adenocarcinoma patients and paired adjacent normal lung tissues were included in this study. Differential proteins and phosphorylated proteins in tumor tissues compared with normal lung tissues adjacent to cancer were identified by mass spectrometry and phosphorylation mass spectrometry. They were verified in large-scale independent samples by Western blot and

enzyme-linked immunosorbent assay (ELISA), The molecular mechanism of tumor markers was further studied by molecular biological methods.

Results: through in-depth analysis of protein expression profile and phosphorylation post-translational modification profile, a total of 11119 gene end products and 22564 phosphorylation modification sites were finally identified. At the same time, clinical information and genomic feature data were integrated and analyzed, and a proteome based Panoramic Map of lung adenocarcinoma was constructed. The study also systematically revealed the proteomic characteristics of people with good and poor prognosis of lung adenocarcinoma, and found that lung adenocarcinoma with good prognosis was closely related to molecular biological processes such as fatty acid metabolism and oxidative phosphorylation, while lung adenocarcinoma with poor prognosis was mainly related to tumor epithelial mesenchymal transformation. And further revealed the protein molecular characteristics of TP53 and EGFR, the two major gene mutations of lung adenocarcinoma in China. The representative marker Hsp90 AB1 was confirmed by plasma samples of independent populations, and it was found that its protein concentration was closely related to poor prognosis. Knockdown of hsp90ab1 in lung cancer cell lines can affect the cycle and apoptosis of lung cancer cells by phosphorylating key proteins.

Conclusion: This study is the first time to systematically depict the molecular map of lung adenocarcinoma at the protein level, and to find the molecular features closely related to the prognosis of patients. This work provides important clues for understanding the occurrence and development of lung adenocarcinoma through multi omics integration analysis, and also lays a transformation foundation for the development of precision medicine and clinical treatment of lung adenocarcinoma in the future.

S2-7

Airborne $PM_{2.5}$ Exposome and Cardiovascular Health: A Population-based Integrated Methodology Establishment and Application.

Prof. Tiantian Li

Chinese Center for Disease Control and Prevention, China

Biography

Dr. Tiantian Li is the director of the Department of Environmental Health Risk Assessment, National Institute of Environmental Health, China CDC. Her major research interests include air pollution, climate

and health. Dr. Li has been the PI for more than 10 national, provincial or ministerial level scientific research projects. She has published more than 100 SCI papers as the first/corresponding author on Nature Climate

Change, Lancet Public Health, Lancet Planetary Health, Science Advances, Circulation, JACC, EHP and etc. Dr. Li won National Special Support Program for National High-level Young Talents in 2014.

Abstract

The Global Burden of Disease (GBD) Study 2019 showed that there were nearly 4.14 million excess deaths related to $PM_{2.5}$ globally, of which 2.48 million were caused by cardiovascular disease. Previous toxicology studies have confirmed the toxicity of $PM_{2.5}$ components. However, epidemiological studies have only found that common components in $PM_{2.5}$ have cardiovascular effects. Recent studies have detected large amounts of low-concentration organic components in $PM_{2.5}$. These $PM_{2.5}$ components have a wide range of sources and are closely related to people's production and life, which can be called airborne $PM_{2.5}$ exposome. The current study lacks the epidemiological integrated methodology of the population-based study of the association of airborne $PM_{2.5}$ exposome with cardiovascular health, so there is an urgent need to establish a population-based integrated methodology to elucidate the effect of airborne $PM_{2.5}$ exposome on cardiovascular health and identify the key components. We established a systematic integrated methodology for airborne exposomes and cardiovascular indicators, and apply this integrated methodology to the population, using QTc interval as an example, to elucidate the mixtures effect of airborne $PM_{2.5}$ exposome, and to further identify key organic components. We detected 224 organic components in $PM_{2.5}$, and those with detection rates greater than 80% were included in the statistical analysis. Mixtures effects from multiple organic components and independent effects from selected organic components on QTC interval were identified and validated. Among the eight key organic components (i.e., TCIPP, BHT-CHO, DnBA/DiBA, BP3, IPP, UV-328 and TPIB) associated with QTC interval prolongation and adverse changes of cardiovascular biomarkers, TCIPP, DnBA/DiBA and BHT-CHO were finally screened out as potential exposure markers for the population health effect. Our findings could provide the latest scientific evidence for the cardiovascular health risks of exposure to airborne $PM_{2.5}$ exposome and highlight the important contributions of organic components of $PM_{2.5}$ to the risks of cardiovascular diseases.

S2-8

Integrated-Studies Interpreted Oligophagous Butterfly Tolerate to Strong Mutagen Aristolochic Acids.

Prof. Yang Luan

Shanghai Jiao Tong University, China

Biography

Dr. Yang Luan received her Ph.D. in 2003 from the Shenyang Pharmaceutical University, worked as a post-doctoral fellow in the NIHS, Japan from 2003 to 2006. She began her scientific career in toxicology in 2006 at Shanghai Institute of Material Medical, joined Shanghai Jiaotong University in 2013. Dr. Luan's research program is focused on utilizing appropriate in vivo and in vitro mutation assays and biological and -omics techniques to provide key toxicological information for exogenous chemicals, including environmental pollutants and herbal medicine, and developing potential biomarkers on genotoxicity, developing new technology on whole genome-widely ultra-low frequencies mutation sequencing. She is the Regional Editor of *Mutation Research - Genetic Toxicology* and *Environmental Mutagenesis*, and editorial member of *Mutagenesis, Genes &Environment*. She participated in OECD genotoxicity guidelines developing as a group member and has been involved the work of international genotoxicity testing expert working group (IWGT) .

Abstract

Herbal medicines containing aristolochic acids (AAs) have drawn great attention in recent years, due to their carcinogenic potential. The carcinogenic effects of AAs are generally considered to result from their metabolic activation to reactive intermediates, and the consequent formation of DNA adducts and induction of gene mutation. However, the underlying mechanisms of their bioactivation have not been fully elucidated. In the present study, aristolochiaceae-feeding swallowtail butterflies *P. aristolochiae* was studied to investigate their AAs-toxicity tolerance mechanisms. *P. polytes* that feeds on non-toxic plants was used as the control. Firstly, whole-genome de novo sequencing and assembly were conducted using Oxford Nanopore Technologies, followed by Hi-C analysis and functional annotation of high-quality transcriptomes by Illumina sequencing. We then conducted ADME studies, after the treatment of aristolochic acid I (AAI), AAI and its main metabolites in the body, feces, and osmeterial secretion of the larvae were

quantitated by using LC-MS/MS. ADME results revealed sequester and biotransformation of AAI in *P. aristolochiae*, but not in *P. polytes*. DNA adducts formation is believed as molecular initiating event of AAs-induced carcinogenesis. DNA adducts results revealed the metabolic activation of AAI in *P. aristolochiae*, and the consequent dA-AAI/II and dG-AAI/II formation were observed in larvae, pupa and imago but not in embryo stage, and the level increased during the entire life cycle, with the DNA adducts level in imagos was about 3 times higher of larvae. To better understand the molecular mechanisms, the transcriptome of larvae were sequenced before and after AAI treatment, and differentially expressed genes (DEGs) were identified. KEGG pathway analysis showed that DEGs were enriched in the metabolic pathways, the biosynthesis of secondary metabolites, and the DNA damage and repair. Candidate genes including nitroreductase, organic cation transporters, and DNA repair genes were identified. Comparative genomic analysis between the *P. polytes* and *P. aristolochiae* revealed mutation or deletion on some candidate genes, suggesting the consequence of evolution for *P. aristolochiae* to tolerate the toxicity from AAs. To reveal the mechanism underlying how *P. aristolochiae* repaired the AAs-induced DNA lesion and maintain its genome integrity for stable heredity, we sequenced the transcriptome of *P. aristolochiae* at embryo, larva, pupa and imago stage, moreover, we investigated the spatiotemporal dynamics of germ cells versus somatic cells in the testis of adult *P. aristolochiae*. Our findings may provide basis for the underlying molecular mechanisms of AAs toxicity in humans.

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