Identification of Chemical-Single Nucleotide Polymorphism-Disease Linkages Implicated in Gene-Environment Interactions

Kosnik, M. B.; Fantke, P.

Published in:
SOT Annual Meeting and ToxExpo 2022

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

used to assess metabolism; however, the high-throughput nature of this MPS is somewhat dampened by the need for replicates of each condition to compensate for high variability. *This abstract does not represent policy or product endorsement by TEX-VAL Consortium member organizations American Chemistry Council, Bristol-Myers Squibb, Merck KGaA, National Institute of Environmental Health Sciences, Sanofi-Aventis, Unilever, and US EPA.*

4640 Association of Demographic Susceptibilities to Metabolic Polymorphisms Potentially Affecting the Efficacy of the Anti-Malarial Drug Artemether

S. Reddy, T. Chang, R. Herabat, A. Vehlow, Q. Nguyen, and D. E. Johnson. *University of California Berkeley, Berkeley, CA.*

Malaria is a life-threatening disease caused by parasites that are transmitted to people through female *Anopheles* mosquitoes, with a reported estimate of around 7.6 million deaths and 1.5 billion cases between 2000-2019. The antimalarial activity of artemether and other artemisinin derivatives is a result of the peroxide bridge found in the active metabolite dihydroartemisinin. This process is mediated by two cytochrome P450 enzymes, CYP3A4 and CYP3A5. This study investigates whether the efficacy or toxicity of the antimalarial Artemether is affected by genetic polymorphisms in enzymes in its drug metabolic pathway and if different demographics are more susceptible. Online databases and genomic platforms were used to identify single nucleotide polymorphisms (SNPs) that that would potentially affect the efficacy of Artemether by (1) lowering its enzymatic activity/function (i.e poor metabolizer), (2) directly causing an adverse metabolic response (i.e toxic effects), or (3) are more prevalent in certain demographic groups. These findings were compared to those of a positive and negative control group and a graphical demographic breakdown of population susceptibility to genetic polymorphisms affecting the performance of Artemether was generated. The results showed that at least seven of the CYP3A allele polymorphisms potentially decrease pharmacokinetic (PK) effects in CYP3A metabolism and *in vitro* enzymatic rates of artemether. Allele polymorphisms vary between populations: polymorphism CYP3A5*3 is prevalent among Caucasians and Asians, while polymorphism CYP3A4*1B is most common among African populations. These results indicate that the CYP polymorphisms investigated in this study may be linked to Artemether efficacy and may provide a better understanding of its ability to treat malaria in different populations.

4641 AhR Signaling Pathway Plays an Important Part in Cellular Response to Oxidative Stress

Z. Kou, W. Dai, R. Yang, and B. H. Choi. *NYU School of Medicine, New York, NY.*
Sponsor: M. Costa

Aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor best known for its role in mediating toxicological responses after exposure to xenobiotic compounds. AhR also plays an essential role in normal development, metabolic homeostasis, and immune functions. Dysregulated AhR signaling pathway is associated with various pathological conditions including cancer. We have recently shown that AhR was activated after cells were exposed to oxidative stress. In particular, serum-containing medium pre-incubated with hydrogen peroxide (H_2O_2) rapidly increased the AhR protein level, as well as expression of cytochrome P450 superfamily enzymes such as CYP1A2 in various cells. Expression of CYP1A2 induced by the H_2O_2-treated medium was AhR-dependent as the induction was completed suppressed by CH233191, an AhR antagonist. The induction kinetics of CYP1A2 by H_2O_2-treated medium was similar to that of 6-Formylindolo[3,2-b] carbazole (FICZ), one of the most potent AhR ligands known to date. Moreover, we have shown that hexavalent chromium [Cr(VI)] treatment induced expression of CYP1A2 in a time- and concentration-dependent manner in HaCaT cells and that Cr(VI)-induced expression of CYP1A2 was also AhR-dependent. Given that Cr(VI) is known to induce reactive oxygen species (ROS) *in vivo*, we postulate that superoxide, a form of ROS induced by Cr(VI) treatment, can be rapidly converted *in vivo* by superoxide dismutase to H_2O_2, which in turn elicits the generation of an AhR ligand(s). In conclusion, our studies suggest that AhR signaling pathway is an integral part of cellular responses to the oxidative stress.

4642 Combined Cytotoxicity and Genotoxicity Evaluation of Nicotine and NNK on BEAS-2B Cells Stably Expressing Human Cytochrome P450 2A13

Y. Sun[1,2], S. Han[1], H. Wang[1], H. Chen[1], H. Hou[1], and Q. Hu[1]. *[1]China National Tobacco Quality Supervision and Test Center, Zhengzhou, China; and [2]Hunan Normal University, Changsha, China.* Sponsor: Q. Meng

Nicotine is the addictive ingredient of tobacco smoke, 4-(methylNitrosamino)-1-(3-Pyridyl)-1-butanone (NNK) is formed mainly by nitrification of nicotine during the later stages of tobacco processing, such as baking and fermentation, both of them exist in cigarette smoke at the same time. Recent studies have shown that nicotine can prevent NNK-induced DNA damage in liver cell lines, possibly by inhibiting CYP enzymes. This observation raises the possibility of interaction between nicotine and NNK bioactivation mechanisms. Therefore, in this study, we used lentivirus system to establish CYP2A13 was stably over-expressed in immortalized human bronchial epithelial BEAS-2B cells (B-2A13). BEAS-2B cells that were transfected with vector (B-vector) and BEAS-2B cells were used as a control. CCK-8 results showed that NNK dose-dependent induced b-2A13 cytotoxicity, and the increase of γH2AX fluorescence focus and micronucleus number also indicated genetic toxicity. These effects were almost completely suppressed by 1000μM nicotine. Together, these findings suggest that CYP2A13 plays an important role in NNK-induced cytotoxicity and genotoxicity, and emphasize that nicotine can reduce this toxicological risk by inhibiting CYP enzymes.

4643 Identification of Chemical-Single Nucleotide Polymorphism-Disease Linkages Implicated in Gene-Environment Interactions

M. B. Kosnik, and P. Fantke. *Danmarks Tekniske Universitet, Kongens Lyngby, Denmark.*

Interactions between environmental factors and genetics underlie the majority of chronic human diseases. However, connecting chemicals, single nucleotide polymorphisms (SNPs), and diseases to assess how chemicals exert effects through gene-environment (GxE) interactions often depends on highly exposed cohorts, which are usually not available. To address this challenge, we used big data integration to form Chemical-SNP-Disease linkages to elucidate possible GxE interactions in human populations. Gene enrichment was used to connect chemical activity data (e.g., Tox21/ToxCast data), to disease endpoints (e.g., from Dose Ontology), to form significant Chemical-Disease enrichments ($p < 0.001$). We postulate that, if Chemical A acts on Gene B to induce Disease C, SNPs on Gene B and implicated in Disease C (from genome-wide association studies, GWAS) may be acted on by Chemical A to contribute to differential disease progression in a population. Based on this adaptation of Swanson's ABC model, Chemical-SNP-Disease linkages were formed between Chemical-Disease enrichments and SNPs (from DisGeNET). As noncoding genetic regions are also important in disease development, intergenic SNPs in linkage disequilibrium with the intragenic SNPs were also curated. This integration formed 25,894,528 Chemical-SNP-Disease linkages across 7,593 chemicals, 55,356 SNPs, and 1,332 diseases. To assess the utility of this resource, SNPs implicated in three clusters of chemicals with different insecticidal modes of action (MoAs) were analyzed: acetylcholinesterase inhibitors (78 chemicals), GABA-gated chloride channel blockers (18 chemicals), and sodium channel modulators (31 chemicals). There were significant differences in the potential for GxE interactions (based on implicated SNPs) between clusters. For example, despite having the fewest chemicals, the GABA group implicated the most SNPs (6846), meaning these insecticides may contribute more to GxE interactions. Additionally, enriched pathways for each MoA (identified using SNPs) significantly differed. This analysis demonstrates how insecticides may have different risk for GxE interactions based on MoA, and how the resource and methods we built can identify specific genetic regions and pathways implicated in differential population susceptibility to characterize GxE interactions for chemical exposures, using MoA or other chemical predictors, in support of chemical risk assessment.

4644 Towards Characterizing the Galaxies of Biosolids Chemical Classes across the Chemical Universe

P. M. Kruse, and C. L. Ring. *US EPA, Research Triangle Park, NC.*

Municipal wastewater treatment in the United States produces an estimated 8 million tons of biosolids yearly. Anthropogenic chemical contaminants in wastewater may accumulate in biosolids. Screening chemicals for potential risk and prioritizing those with the greatest likelihood of adverse outcomes to human and ecological health is important for mitigating the damage associated with their presence in biosolids. Thus, biosolids (land-applied, landfilled, or incinerated) are of interest for high-throughput (HT) risk-based screening and prioritization of chemicals. Risk-based screening and prioritization requires estimates of chemical-specific exposure, which in turn requires information on the concentrations of chemicals in biosolids. With only limited data on concentrations available, we propose to develop an HT machine-learning consensus model to predict biosolids chemical occurrence. With relatively limited availability of biosolids chemical concentration data, however, the chemical domain of applicability of the model will be limited by the chemical space represented by the training data. Here, we characterize that chemical space as defined by chemical class. The National Sewage Sludge Surveys (NSSS) of 1988, 2001, and 2009 are our main sources of biosolids chemical concentration data. Up to now the complete survey data from 1988 has been inaccessible due to outdated data storage technology; we extracted this data from scans of archived print copies. We then characterized the chemical classes represented by the analytes from these surveys using a publicly available chemical hierarchy tool, ClassyFire, and compared them to the chemical classes of compounds on the Toxic Substances Control Act (TSCA) Chemical Substances Inventory and to the "universe" of chemical classes defined by ClassyFire. The NSSS data represent 744 chemicals over 75 chemical classes. As of September 2021, these classes represent 22.9 percent of chemical classes represented by chemicals on the TSCA Inventory, and 9.79 percent of chemical classes in the chemical space defined in ClassyFire. Our results are important not only for determining the domain of