A population-based approach to assess inter-individual variability in chemical metabolism

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Wednesday, October 26, 2016
2301 McGavran-Greenberg Hall
12:20 – 1:10 p.m.

Abstract:
One of the many challenges in environmental health sciences is addressing human variability in adverse effects from exposure to chemicals. Traditional toxicity testing is conducted with a single isogenic strain of laboratory animals to investigate health effects from chemical exposures; thus, assessing genetic susceptibility to toxicity in such studies is impossible. One approach to address inter-individual variability in humans is by using a mouse diversity panel – a collection of genetically-diverse mice to assess variability in toxicity responses and identify causal genes driving such variability by genome-wide association analysis. The underlying hypothesis for this approach is that genetic variability plays a role in inter-individual differences in chemical metabolism and concentration-effects. This study aimed to test this hypothesis using trichloroethylene (TCE) as a case study chemical. Adult male mice from 50 Collaborative Cross (CC) strains were exposed to a single dose of TCE and both metabolism and concentration-effect responses were collected. Inter-individual variability in protein and activity levels of TCE-metabolizing enzymes were found to be less variable across the mouse population. TCE concentration-effects' responses were found to highly variable (more than 10-fold) across strains. Interestingly, we observed positive association between TCE metabolism and concentration-time responses across the CC population. Further, genome-wide analysis revealed novel genetic variability in TCE metabolism and effects. Together with other studies, our work identifies novel genetic determinants of variability in TCE metabolism and effects, establishes a range of inter-individual variability in concentration-time and concentration-effects responses, and demonstrates the feasibility and utility of integrating mechanistic toxicology studies with population-based study designs that enable characterization of the variability in responses with chemical exposures.