

Linking inflammation with environmental exposures

By Tara Ann Cartwright

A Dec. 11 webcast seminar highlighted the current research on inflammation by National Toxicology Program (NTP) scientists. This important disease process is the focus of a cross-divisional faculty at NIEHS, established pursuant to the 2012-2017 NIEHS Strategic Plan. Andrew Rooney, Ph.D., deputy director of the NTP Office of Health Assessment and Translation, and Nicole Kleinstreuer, Ph.D., a contractor who supports the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, spoke on “Analysis and Predictive Toxicology Methods at NTP to Identify Biomarkers of Inflammation.”

Mamta Behl, Ph.D., a toxicologist in the NTP General Toxicology and Cancer Group, introduced both speakers. “The role of environmentally induced inflammation in health outcomes is an issue of longstanding interest to NIEHS and NTP and is very challenging in its scope,” she said.

Atherosclerosis — an answerable question

Chronic inflammation, which is also known as low-grade or systemic inflammation, is linked to numerous health effects and disease states. Despite the enormous interest of researchers, the details of this link remain unclear. According to Rooney, because of the large number of health effects and the vast literature on the subject, researchers are challenged to develop an answerable question related to linking exposure, the resulting inflammation, and ultimately, a health effect.

Rooney’s team set out to identify a single health effect with a manageable literature base, so they could evaluate the evidence using state-of-the-art analyses. Atherosclerosis, which has both a clear inflammatory mechanism associated with a range of environmental contaminants and a significant public health impact, satisfied their criteria.

Rooney’s strategy involved a two-pronged approach — the first was a systematic literature review process (see related [summary](#)) to evaluate evidence for the association between environmental exposures and biomarkers of inflammation, and the second was development of an adverse outcome pathway. The pathway approach describes molecular events between environmental exposure and a resulting adverse health outcome.

Rooney stressed that this project also evaluates the utility of the adverse outcome pathway as a tool. More importantly, the researchers hope to identify biomarkers of key events for use in future studies.

High-throughput screening

Kleinstreuer reported on how high-throughput screening data, as used in the U.S. Environmental Protection Agency’s [ToxCast](http://www.epa.gov/ncct/toxcast/) (<http://www.epa.gov/ncct/toxcast/>) program, can be combined with literature review approaches to characterize the inflammatory pathway and identify biomarkers of environmental chemical exposure associated with inflammation-mediated adverse health outcomes.



Rooney’s team is evaluating evidence that environmentally induced inflammation leads to serious health effects, including atherosclerosis. (Photo courtesy of Steve McCaw)



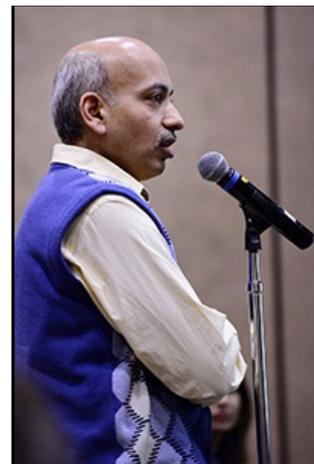
Kleinstreuer uses ToxCast Phase II data to help develop and test adverse outcome pathways for inflammation-driven health effects. (Photo courtesy of Steve McCaw)

To identify biomarkers, researchers stimulate human primary cells with various cytokine mixtures to mimic the tissue environment following chemical exposure. The scientists measure changes in expression of inflammatory and anti-inflammatory molecules.

According to Kleinstreuer, the aryl hydrocarbon receptor (AHR) showed promise. “A very small literature search shows that certain chemicals, such as polycyclic aromatic hydrocarbons, may trigger AHR to increase expression of certain cytokines, contributing to development of inflammation and atherosclerotic plaque formation,” she said, linking the predictive model with published research.

Primary human cell cultures used in predictive models may help establish a link between exposure to pollutants and the inflammatory pathway, Kleinstreuer noted in closing. “In tandem with the work [Rooney] is doing in systematic review of the literature, these tools and analyses are crucial to developing and testing an adverse outcome pathway for atherosclerosis,” she said.

(Tara Ann Cartwright, Ph.D., is a former postdoctoral fellow in the NIEHS Intracellular Regulation Group).



The format allowed ample time for attendees, both in person and via webcast, to raise questions on the work by Rooney and Kleinstreuer. Kyathanahalli Janardhan, Ph.D., is a pathologist in the NTP Immunohistochemistry Laboratory. (Photo courtesy of Steve McCaw)

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