A new approach to determine cancer risk of chemicals

By Sara Mishamandani

A new study by NIEHS-funded researchers at Boston University (BU) and the NIEHS National Toxicology Program (NTP) has shown that computational models of short-term exposure to a chemical can predict long-term cancer risk. The study,
(http://www.ncbi.nlm.nih.gov/pubmed/25058030)
led by computational biologist Stefano Monti, Ph.D., an associate professor at BU, is a step toward simpler and cheaper tests to screen chemicals for cancer risk.

In September 2013, Monti visited NIEHS and described his latest work to develop a model for predicting toxicity and carcinogenicity. From left, NIEHS SRP Director Bill Suk, Ph.D.; NIEHS SRP Program Administrator Heather Henry, Ph.D.; Monti; and NTP Biomolecular Screening Branch (BSB) head Raymond Tice, Ph.D., discussed the implications of the findings for advancing predictive toxicology. (Photo courtesy of Heather Henry)

The current gold standard for testing chemicals for cancer risk is a 2-year rodent bioassay, which can cost $2 million to $4 million per chemical to complete. As a result, less than 2 percent of the approximately 84,000 chemicals in commercial use have gone through standard carcinogenicity testing.

"Not enough attention is given to understanding chemicals before they are used by industry and released into the environment," said Monti.
(http://www.bumc.bu.edu/medicine/faculty/monti/)
"This work has confirmed that it is possible to predict the long-term cancer risk by measuring the short-term effects."

Understanding response to chemicals in the body

According to the authors, high-throughput genomic approaches have been applied to understand how cancer is initiated and progresses, to identify therapeutic targets, and to discover biological markers of cancer. However, using these methods to study environmental causes of cancer has not received as much attention.

Auerbach is a member of the NIEHS Molecular Toxicology and Informatics Group within BSB. He is responsible for oversight of the NTP DrugMatrix database and ToxFX toxicogenomics analysis tool. (Photo courtesy of Steve McCaw)

Researchers at BU teamed up with NTP molecular toxicologist Scott Auerbach, Ph.D., to build on current genomic analysis technologies and develop affordable approaches to predict carcinogenicity and toxicity of thousands of environmental chemicals and mixtures. As part of this effort, BU Superfund Research Program (SRP) Center Director David Sherr, Ph.D.,
(http://www.busrp.org/)
and Monti are developing a platform for predicting chemical toxicity and carcinogenicity.

Using a data set from the NTP DrugMatrix
(https://ntp.niehs.nih.gov/drugmatrix/index.html)
database, researchers compared gene expression responses to known carcinogens and noncarcinogens. From the data, they developed a predictive model to discriminate between the two. They also identified differentially expressed genes associated with cancer-causing chemicals and were able to zoom in on the potential mechanisms driving the initiation of cancer.

Moving forward

In the study, the researchers validated the model to predict carcinogenicity, using two large, rat-based gene datasets. They found that carcinogenicity predictions depend on the tissue exposed to the chemical of interest and confirmed and expanded on several previous studies implicating DNA damage, the aryl hydrocarbon receptor, and other pathways in the response to carcinogen exposure.

To their knowledge, the data collection they assembled represents the largest toxicogenomics resource analyzed to date. The collection allows the scientists to continue to evaluate issues related to variability in studies, differences due to tissue, exposure dose and length, sample size, and other factors, to achieve the maximum predictive accuracy using the model.

According to the authors, despite an overall decrease in incidence of and mortality from cancer, about 40 percent of Americans will be diagnosed with the disease in their lifetime, and around 20 percent will die of it. By further developing this platform for use, researchers will be able to better predict carcinogenicity and understand the biological process and pathways affected by exposure to different chemicals.

Citation: Gusenleitner D, Auerbach SS, Melia T, Gomez HF, Sherr DH, Monti S.
(http://www.ncbi.nlm.nih.gov/pubmed/25058030)
2014. Genomic models of short-term exposure accurately predict long-term chemical carcinogenicity and identify putative mechanisms of action. PLoS One 9(7):e102579.

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