New test provides accurate measure of DNA damage from chemical compounds

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A new biomarker test developed by researchers at Georgetown Lombardi Comprehensive Cancer Center and their colleagues can help predict, with up to 90 percent certainty, which chemical compounds can cause DNA damage that could lead to cancer. The study was published early online the week of December 4, 2017, in *PNAS*.

Current laboratory tests that assess potential toxicity in humans due to exposure to chemical compounds often result in a high number of false-positive findings for agents that can induce DNA damage. Many of these positive results may reflect cellular toxicity at high chemical doses rather than actual genotoxicity (damage to DNA or genes). Such false-positive results often lead to expensive and time-consuming follow-up testing.

The lack of an accurate, rapid and high-throughput test that assesses genotoxicity has been a major bottleneck in the development of new drugs as well as the testing of substances by chemical, cosmetic, and agricultural companies, says Albert J. Fornace Jr., MD, professor in the departments of biochemistry and molecular & cellular biology, oncology and radiation medicine at Georgetown University School of Medicine, and a member of Georgetown Lombardi Comprehensive Cancer Center.

Compounding this need is the fact that thousands of chemicals already in use that have had little, if any, toxicologic assessment, he adds.

"In addition, there is an increasing mandate to reduce animal testing," Fornace says, pointing out that in the European Union, animal testing for ingredients in cosmetic products is already prohibited.

The new test, a biomarker panel referred to as TGx-DDI, is based on genes that are actively transcribed, or expressed, in a cell. These genes reflect particular pathways that respond to various types of stress, and can provide more insight into how cells respond to a particular type of injury, particularly damage to DNA. While there have been many studies that have used gene expression to measure injury responses, a key feature of the current approach is the development of a biomarker panel of genes that can identify stress due to DNA damage. Having developed the robust biomarker panel, a consortium of academic, government, and industry investigators, organized by the Health and Environment Science Institute, a global non-profit, selected many chemicals and drugs,

representing different classes of toxicants, to test. The chemicals included known DNA-damaging agents, chemicals known to be negative for genotoxicity and not cancer causing, and chemicals known not to cause cancer, but which tested positive in older lab genotoxicity assays.

All of the DNA-damaging agents tested positive with the new assay. All of the chemicals known to be negative for genotoxicity and that were not cancer causing tested negative. Importantly, 9 out of 10 results were negative for chemicals known not to be cancer causing but that showed a positive result in conventional lab genotoxicity tests.

"Compared to older tests, our approach allows for very accurate and high-throughput screening of chemical compounds that cause DNA damage, and potentially, cancer in humans," concluded Fornace.

More information: Heng-Hong Li el al., "Development and validation of a high-throughput transcriptomic biomarker to address 21st century genetic toxicology needs," *PNAS* (2017). www.pnas.org/cgi/doi/10.1073/pnas.1714109114

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