Potential Mitochondrial Toxicants

Tox21 Screen Identifies Structures of Interest

Mitochondria have many important functions, including production of adenosine triphosphate (ATP) to fuel cells and regulation of cell growth, signaling, differentiation, and apoptosis.1 Disrupted mitochondrial function raises the potential for health effects and in fact has been associated with cancer, diabetes, cardiovascular disease, and autism.2,3 In a study reported this month in EHP, investigators with the Tox21 consortium assessed the impact of more than 8,300 chemicals on mitochondrial activity.4

Tox21, short for Toxicology in the 21st Century, is a collaboration of federal entities including the National Toxicology Program, the Environmental Protection Agency, the Food and Drug Administration, and the National Center for Advancing Translational Sciences (NCATS). One product of Tox21 to date is a library of more than 10,000 chemical samples comprising 8,312 unique substances. These samples include industrial chemicals, consumer products, food additives, and human and veterinary drugs.5

The Tox21 robotic system loads chemical samples and cells into 1,536-well microtiter plates; then the cells are scanned for specific changes.4 For this current study, researchers measured mitochondrial membrane potential (MMP) and intracellular ATP content in human hepatocellular carcinoma cells exposed to a variety of reasons. Of these, 17% showed evidence of cytotoxicity.6

MMP serves as a marker for both mitochondrial function and cell viability.4 Changes to intracellular ATP content can be used to detect activities of adenosine triphosphate (ATP) to fuel cells and regulation of mitochondrial bioenergetics. Changes to intracellular ATP content can be used to detect activities of ATP synthase.7

Of the chemicals tested, 11% decreased MMP (but with no apparent effect on cell viability), 65% were inactive, and 3% increased MMP. The remaining 21% of the chemicals gave inconclusive results for a variety of reasons. Of these, 17% showed evidence of cytotoxicity.4

Some results paralleled previously identified mechanisms of toxicity for chemicals. For example, triethyltin bromide, which is already known to interrupt ATP production,7 also proved to be one of the most potent suppressors of MMP.4

Structure–activity relationship analysis gave clues about how other chemicals may reduce MMP. Recurring structural features associated with decreased MMP included a substituted phenol moiety, a nitro- benzene core, and a thiazole substructure.4 “The cell model employed casts a broader net for defining mitochondrial toxicity to include changes. Some will also be tested in Caenorhabditis elegans (roundworms) and mitochondrial gene microarrays. The combined results will help guide the selection of compounds for in-depth animal studies.”

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