Toxicity testing in the 21st century—a vision and a strategy

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The future of toxicology will depend on how well cutting-edge technology is transferred and integrated to solve problems in toxicology. Toxicity testing is poised to take advantage of the revolutions in biology and biotechnology. In 2007, the National Research Council of the US National Academies published a report, entitled Toxicity Testing in the 21st Century: A Vision and a Strategy, which advocates the use of these new technologies to transform toxicity testing from a system based on whole-animal testing to one founded mainly on in vitro methods that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin. This report concluded that a transformative paradigm shift was needed to confront the many issues faced in the toxicity testing of environmental chemicals, drugs, and cosmetics to which humans are exposed. Toxicity testing, as envisioned by this NAS report, involved the interplay of toxicity pathways, targeted testing, chemical characterization, dose-response and extrapolation modeling, population and exposure data, and risk assessment. This lecture will present key elements of this report, along with selected examples of studies and discussions in the scientific literature, which evaluate new approaches in toxicity testing.

Cellular adaptive response to environmental toxicants and other noxious stimuli

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Living organisms are constantly subjected to diverse types of stress both external and internal sources. While excessive stress leads to necrotic or apoptotic death, moderate amounts of noxious stimuli may render the cells adaptive or tolerant to ongoing or subsequent insults. Such adaptive survival response normally accompanies de novo synthesis of proteins through activation of distinct stress-responsive signaling. One of the key signaling molecules involved in cellular adaptation or tolerance to a wide array of noxious stimuli is nuclear transcription factor erythroid 2p45 (NF-E2)-related factor 2 (Nrf2). Our previous studies have revealed that Nrf2 plays a pivotal role in cellular stress response. Nrf2 is sequestered in the cytoplasm as an inactive complex with the inhibitory protein Keap1. Upon activation, Nrf2 binds to antioxidant responsive element (ARE) or electrophile responsive element (EpRE), leading to the coordinated up-regulation of down-stream target genes that boost cellular antioxidant/cytoprotective potential. Many chemopreventive natural products can induce ARE/EpRE-driven upregulation of antioxidant/phase-2 detoxifying enzymes or other cytoprotective proteins, thereby fortifying cellular defence against oxidative, nitrosative and inflammatory insults. Cysteine thiols present in Keap1 functions as a redox sensor in transcriptional regulation of a distinct set of stress responsive/cytoprotective proteins. Some chemopreventive/chemoprotective natural products can induce ARE/EpRE-driven upregulation of cytoprotective gene expression, thereby fortifying cellular defence against oxidative, nitrosative and inflammatory insults. Supported by the Global Core Research Center (GCRC) grant, National Research Foundation-MEST, Republic of Korea.