Mapping Tox21/ToxCast HTS Data to Key Characteristics of Carcinogens

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The 10 key characteristics of carcinogens (KCCs) were developed by assessing common features of human carcinogens, or agents that induce cancer. Carcinogens typically express one or more KCC, and the KCC concept leverages mechanistic evidence to comprehensively evaluate cancer hazard for a chemical. Using this concept, high-throughput screening (HTS) assays can be reviewed in the context of the 10 KCCs. HTS assays have revolutionized toxicity testing, and federal programs like the Toxicity Testing in the 21st Century (Tox21) federal consortium and the U.S. Environmental Protection Agency's Toxicity Forecaster (ToxCast) have been leading efforts to make bioactivity data publicly accessible. Availability of data from over 10,000 chemicals and thousands of assay endpoints targeting molecular and cellular responses presents an unparalleled opportunity to address critical gaps in mechanistic evidence and provide additional insight for applying the KCC principle. In this work, mappings of Tox21/ToxCast assays were evaluated to assess relevance for informing on one or more KCCs. A panel of mechanistic toxicology experts, including some from regulatory agencies, subsequently reviewed the KCC mapping to ensure their accuracy and reliability, producing a final consensus. Upon completion, a comprehensive list of KCC-mapped HTS assays will be publicly available, facilitating the application for mechanistic cancer hazard assessment and a deeper understanding of chemical carcinogenesis. This effort will be incorporated into the Integrated Chemical Environment (ICE: https://ice.ntp.niehs.nih.gov/) and in the IARC Monographs for identification of cancer hazard. This project was funded with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.