REDOX DISRUPTING POTENTIAL OF TOXCAST CHEMICALS RANKED BY ACTIVITY IN MOUSE EMBRYONIC STEM CELLS

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To gain insight regarding the adverse outcome pathways leading to developmental toxicity following exposure to chemicals, we evaluated ToxCast™ Phase I chemicals in an adherent mouse embryonic stem cell (mESC) assay and identified a redox sensitive pathway that correlated with altered myocardial differentiation. Here, we developed a weight-of-evidence ToxPi ranking for 309 chemicals across 19 ToxCast assays selected for cell-based and biochemical features that can be tied to cellular redox balance. Among the highest ranking putative redox disrupting chemicals (pRDC) were mitochondrial disruptors such as rotenone, azoxystrobin, pyraclostrobin, fluoxastrobin and trifloxystrobin. For these 5 chemicals, the ToxPi ranking followed their rank order potency in developmental toxicity (ToxRefDB). For the entire chemical library, those that produced a 50% change in stem cell differentiation (AC50) were grouped with more potent pRDCs whereas chemicals that altered cell number by 50% were evenly distributed throughout the redox ToxPi ranking (Wilcoxon rank sum, p=0.03). To test the putative redox disrupting activity of pRDCs, 2',7'-dichlorodihydrofluorescein diacetate was used to measure ROS in exposed mESCs. Preliminary data indicated H_2O_2 at concentrations <300uM produced concentration and temporally-dependent ROS levels. ROS was 30% lower on Day 3 than Day 7, indicating a decline in antioxidant capacity with mESC differentiation. Thus, more differentiated mESCs may have decreased antioxidant capabilities. This finding indicates the importance of temporal considerations in the mESC differentiation assay when interpreting the pRDC ToxPi ranking of ToxCast chemicals on oxidative stress signaling/altered redox pathways. In sum, altered redox potential may be an adverse outcome pathway linked to altered differentiation in mESCs and developmental toxicity in vivo. Identification of pRDCs may be useful in prioritizing chemicals as potential developmental toxicants.
This abstract does not necessarily reflect US EPA policy.