In vitro Predictive Toxicology for Breast Cancer

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Background

• Identifying chemicals that increase breast cancer risk could help reduce incidence
• High throughput (e.g. ToxCast, Tox21) and computational methods can help predict adverse effects
• We are collaborating with EPA and others to develop in vitro methods to predict chemicals that increase breast cancer risk
• Pathways include genotoxicity, hormone disruption

Objectives

• Characterize genotoxicity and nuclear receptor activity of mammary carcinogens and non-carcinogens using publicly-available data
• Assess the effects of metabolic activation on test results
• ID MCs that act through non-genotoxic mechanisms

Chemicals of interest

• MG carcinogens (MCs) caused an increase mammary tumors in at least one animal study (Rudel et al. 2007)
• MG development disruptors (MGdds) induced changes in MG development after early life exposure (Rudel et al. 2011)
• “Non-carcinogens” (nonCs) didn’t increase any tumors in NTP cancer assay

Genotoxicity

NLM’s Chemical Carcinogenicity Research Information System

• “Mutagenicity” tests: Ames + mammalian mutation, chromosomal aberration, micronuclei, unscheduled DNA synthesis, +/- metabolic activation
• Data available for 156 MCs, 22 nonCs
• Varied sources, not comprehensive

Genotoxicity of mammary carcinogens and non-carcinogens

• 90% of MCs active (>15% of entries positive) in some study type
• 8% of MCs consistently negative (20% consistently negative in vitro w/o metabolic activation)
• 54% of nonCs active in some study type
• 46% of nonCs consistently negative

NR activity

Tox21 (Huang et al. 2011) qHTS beta-lactamase reporter gene assays

• Data available for 82 MCs, 16 nonCs
• Variable assay reproducibility - AR antagonist and RXR agonist weakest

Conclusions

• Majority of mammmary carcinogens are genotoxic in bacterial and mammalian cells
• At least 12% of MCs require in vitro metabolic activation or in vivo testing to show genotoxic activity  – lack of MA is an important limitation of high throughput screening so far
• Some MCs likely act through multiple mechanisms (genotox and NR-mediated)
• MCs are more likely to show NR-activity than nonCs

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References


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