Integrating ToxCast Assays into an Androgen Receptor (AR) Pathway Model

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Abstract

The Tox21 and ToxCast programs include multiple *in vitro* assays conducted in a high-throughput screening (HTS) format that are relevant to the AR pathway and can be used to identify substances with potential androgenic/anti-androgenic activity *in vivo*. Here we used a number of assays that map to the androgen receptor (AR) pathway to build a mathematical model that attempts to distinguish true AR pathway activity from technology-specific assay interference. This battery of nine assays (five from ToxCast and four from Tox21) probes perturbations of the AR pathway at multiple points (receptor binding, cofactor recruitment, gene transcription and protein production) in multiple cell types. We compiled a list of putative AR reference chemicals from the ICCVAM (2003) and OECD (2010) reference chemical lists that includes agonists, antagonists, selective androgen receptor modulators (SARMs), and inactive chemicals. The model showed 96% (23/24) concordance across the reference set, including successfully identifying multiple SARMs with both agonist and antagonist activity. However, fluoranthene, a SARM, was active only in the cofactor recruitment assays and was therefore mispredicted by the model as acting via an assay-specific interference pathway. All chemicals in the ToxCast library known to target AR were correctly identified by the model. We will discuss a variety of patterns of assay activity and pathway predictions across 1846 ToxCast chemicals and identify those prioritized to be active against the AR pathway. Where available, we will compare predictions to toxicity data from the literature and look for potential trends relating to use case and exposure scenarios.
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