Predicting Skin Sensitization Using ToxCast Assays

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Abstract

Allergic contact dermatitis (ACD) is an adverse health effect from repeated exposure to skin-sensitizing chemicals and products. To minimize ACD, regulatory authorities require tests, like the murine local lymph node assay (LLNA), to identify potential skin sensitizers. The Organisation for Economic Co-operation and Development (OECD) established an Adverse Outcome Pathway (AOP) for skin sensitization. Many organizations, including the OECD and NICEATM, are pursuing integrated testing strategies using novel *in vitro* and *in silico* approaches to reduce or replace animal use. The U.S. EPA's ToxCast project includes high-throughput screening (HTS) assays in human primary skin cells and other systems that map to key events in the AOP (e.g., oxidative stress, cytokines). We built a cross-validated random forest model using ToxCast data and a balanced training set of 60 chemicals with in vivo LLNA data. The model predicted LLNA results with 80% accuracy, representing the performance against all chemicals when they appear in external test sets. The assays with highest variable importance included known AOP targets (e.g., Nrf2, T-cell proliferation) as well as targets outside the current AOP (e.g., Coll III, PPAR, PXR, ER). Compounds mispredicted by the model were found to be structurally similar, and we will discuss potential enrichment of this approach by incorporating molecular descriptors. Well-characterized AOPs like skin sensitization provide opportunities to use ToxCast HTS data to identify critical biological targets and develop efficient testing strategies that minimize animal use in regulatory testing. *This project was funded in whole or in part with Federal funds from the NIEHS, NIH under Contract No.HHSN27320140003C.*