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Applications Note

Databases and ontologies

sAOP: linking chemical stressors to adverse outcomes pathway networks

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Abstract

Motivation: Adverse outcome pathway (AOP) is a toxicological concept proposed to provide a mechanistic representation of biological perturbation over different layers of biological organization. Although AOPs are by definition chemical-agnostic, many chemical stressors can putatively interfere with one or several AOPs and such information would be relevant for regulatory decision-making.
Results: With the recent development of AOPs networks aiming to facilitate the identification of interactions among AOPs, we developed a stressor-AOP network (sAOP). Using the 'cytotoxitiy burst' (CTB) approach, we mapped bioactive compounds from the ToxCast data to a list of AOPs reported in AOP-Wiki database. With this analysis, a variety of relevant connections between chemicals and AOP components can be identified suggesting multiple effects not observed in the simplified 'one-biological perturbation to one-adverse outcome' model. The results may assist in the prioritization of chemicals to assess risk-based evaluations in the context of human health.
Availability and implementation: sAOP is available at http://saop.cpr.ku.dk
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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Adverse outcome pathway (AOP) is intended to capture existing knowledge, containing empirically based foundations for predicting apical toxicity that are biologically significant and plausible. They proceed through a series of key events (KEs), at different levels of biological organization (cell, tissues and organ), and end in one or more pathological states defined as adverse outcomes AOs (Ankley *et al.*, 2010).

Although one key principle is that AOP represents the chemical-agnostic portion of pathways (independence of any specific chemical) involved in biological perturbation leading to toxicological outcomes, the evidence used to support each KE–KE relationship (KERs) is based on chemical-specific exposure data (Leist *et al.*, 2017). Furthermore, it is observed that some KEs and KERs contribute to several AOPs, and in contrast to the 'one perturbation-one AO' model, the characterization of AOP networks has become more suitable to deal with such complex systems (Knapen *et al.*, 2018).

Therefore, we developed an open access chemical stressor-AOP (sAOP) web application (http://saop.cpr.ku.dk) that gives an overview of chemical perturbance of AOP networks.

2 Materials and methods

To develop the sAOP server, we made use of the ToxCast program (Dix *et al.*, 2007). This program builds large collections of *in vitro*

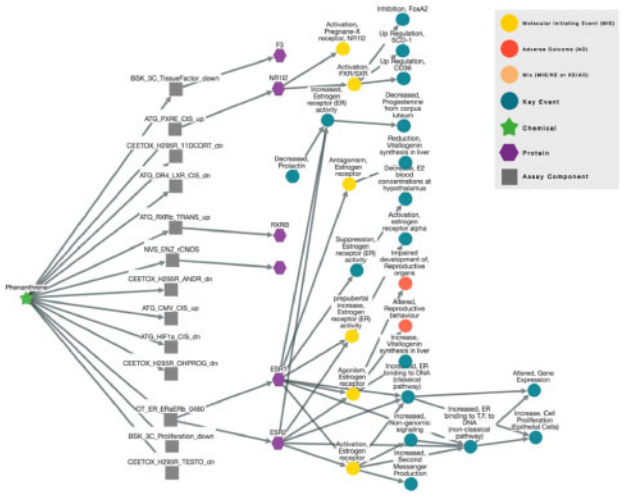

Fig. 1. Results of the sAOP network for the chemical 'phenanthrene'. A color scheme is defined for each element of the network. The arrows show the edges directionality

assay data on a diverse set of chemicals. A filtering step using the cytotoxic-associated burst (CTB) was applied, as it was demonstrated that chemicals activate assays at concentration levels also observed for cytotoxicity or cell stress in ToxCast (Judson *et al.*, 2016). The remaining chemicals showing activities on one of the targets in ToxCast were then mapped to AOPs, collected from AOP-wiki (version as of March 2018), a knowledgebase structure of AOP (Villeneuve *et al.* 2014), resulting to a stressor-AOP network between 4960 chemicals, 369 proteins, 1089 KEs and 207 AOPs. More detailed information is found in the Supplementary Information.

3 Results

Users can query the sAOP database by 'chemicals', 'assay', 'protein', 'Key Event' and 'AOP'. Some parameters can be included in the search such as 'AC50 score', 'z-score' or 'degree of separation' to facilitate the visualization of the network. For example, the search for 'phenanthrene', a polycyclic aromatic hydrocarbon, with a degree of separation of 4, results to a network represented in Figure 1, i.e. 13 assays which show activity on three proteins (ESR1, ESR2 and NR1I2) linked to 6 MIEs, 16 KEs and 2 AOs. More examples are provided in the Supplementary Information.

4 Conclusion

The proposed stressor-AOP network described here allows to explore the knowledge 'space' regarding chemicals and adverse effects from a mechanistic point of view. It can assist with the identification of chemicals involved in an AO and in the prioritization of biological assay endpoints associated to known AOPs. Finally, it suggests how the combination of various toxic compounds can, by affecting the same pathway or different modules of the same AOP, be a sufficient perturbation for the appearance of the AO (Miller *et al.*, 2017). With the interest of regulatory agencies to consider new approach methodologies (NAMs) in risk assessment, such integration could be suitable for regulatory decision-making.

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Conflict of Interest: none declared.

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