Network-based modeling of APAP-induced hepatotoxicity using interactomics and transcriptomics data

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Facts & Figures
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Challenge
Paracetamol (acetaminophen, APAP) overdose alone is estimated to contribute around 40% of all acute liver failure cases in the USA.
• The dose that induces hepatotoxicity in a person varies
• The intrinsic response to APAP differs across patients substantially

TransQST is an international effort to improve the understanding of the safety of medicines via translational quantitative systems toxicology. Within the context of WP4 of TransQST, we aim to model the APAP-induced toxicity affecting liver using a systems biology approach.

Approach & Methodology
We hypothesize that paracetamol induces a dose-dependent hepatotoxic response in the liver through the perturbations of interactions of the drug’s off targets with toxicity-related proteins.

Problem formalization
• Node-weighted Steiner tree that connects given seed nodes through other nodes (S ∈ V’)
• Minimizes the cost associated with including non-seed nodes (argmin V’ |V’ \ S| & argmax V’ \ S |V’ \ S | T’)
• Sets the costs such that drug response genes are easier to be included (w_i = 10^{-|FC_i|})

Results
Adverse outcome phenotypes are manually curated from the literature (using LiverTox, MEDRA And DisGeNET), yielding eight adverse outcomes affecting human liver (see table).

Paracetamol-induced liver toxicity subnetwork is shown below. Nodes are highlighted based on APAP-induced gene expression (high dose, 24h, |FC| >1.5).

3 out of 9 APAP-targets are among 22 included proteins (P = 1.1 × 10^{-6})
• APAP targets: GSTP1, PTGS2, TRPV1
• De novo candidates: HSPA6, RELA, SFN, SQSTM1, TRIM55, TUBA1A

Value of IMI collaboration
This work was possible due to a close collaboration and exchange of ideas as well as data between transQST partners. We especially thank Terezinha de Souza and Joaquim Aguirre-Plans for their help providing data.

Impact & take home message
• Interactome-based modeling offers systematic insights into APAP-induced hepatotoxicity
• The methodology can be seamlessly extended to other adverse outcomes

Data sets
• Liver-specific interactome data from InfBioMap [3]
• Tissue expression for liver from GTEx (TPM > 1) [4]
• Adverse outcome associated genes (seeds) for DILI from DisGeNET based on LiverTox phenotypes [5]
• APAP targets from DrugBank
• APAP-induced gene expression (high dose, 24h from TG-GATES) [7]

References
[3] Li et al., 2017, Nat Methods
[5] Piñero et al., 2016, NAR
[7] Igarashi et al., 2015, NAR

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