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The study of troglitazone liver toxicity via metabolomics and *in silico* approaches

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Background: Troglitazone (TGZ) is a member of thiazolidinedione class of chemicals was developed for the treatment of type 2 diabetes in the late 1990s. TGZ was withdrawn from the market in 2000 due to a number of fatalities due incidence of idiosyncratic liver toxicity. Till date, the mechanism of TGZ-induced liver toxicity is unclear. However, several molecular mechanisms have been proposed to underlie TGZs liver toxicity. Understanding the interactions between these mechanisms could aid drug developers more robustly predict drug-induced liver injury (DILI), a major cause of drug withdrawal.

Aims: To use a combination of in silico and in vitro approaches to examine the interaction of TGZ with multiple biological sequence causative of TGZ hepatoxicity.

Method: In silico, the Petri net software SNOOPY was used to reconstruct the known cellular effects of TGZ, including activation of PPRAy, interaction with mitochondria, activation of apoptosis. The model was imported into the MUFINS software suite and simulated. We tested the apoptotic part of our model and activation of apoptosis was validated against the published SBML model downloaded from BIOMODELS upon which the model was based. We performed in vitro assays to determine the cytotoxic effect of TGZ on liver cancer cell (Huh7 cell).

Results: The model created in SNOOPY and simulated in MUFINS was able to reproduce the behaviour for the original BioModels submission simulated in COPASI, validating the reconstruction. Our in vitro data demonstrate that, TGZ dose dependently decreased Huh7 cell growth and viability, and induced apoptosis in Huh7 cells. Finally, we conducted caspase assays to investigate the mode of the observed cell death and did report that TGZ induced caspase 3/7 activities in a concentration dependent manner. In addition, caspase-9 activities were seen to increase in a concentration-dependent manner, however we did not record capsase-8 activities. These data support activation of apoptosis via the intrinsic route.

Conclusion: The in sillico model reproduces the behaviour of the original model and can therefore be used to explore TGZ induced apoptosis. The in vitro model system can reproduce the known effects of TGZ making it a suitable model for this current study.

Future work: Expand and parameterize the computational model predictive of TGZ toxicity to increase the predictive nature of our model. Explore TGZ metabolic pathways and conduct in vitro assays to validate our model.

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