Abstract #540 | Poster

Quantitative proteomics reveal mechanistic insights into direct and indirect drug-induced thyroid toxicity in rats

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As an endocrine organ, the thyroid regulates various physiological mechanisms in humans, such as individual development, cell proliferation and differentiation, whereby secretion disorders can cause diseases. Several clinical drugs have been described to cause thyroid toxicity (TT) by interfering with the synthesis, transport and metabolism of thyroid hormones (direct TT) or by altering the synthesis and secretion of thyrotropin (indirect TT). However, the underlying mechanism of drug-induced TT (DITT) is not fully understood yet, thus hampering the risk assessment of novel drugs.

Here we applied a quantitative proteomics study to investigate rodent TT, which is a part of a multi-omics study in the framework of the LRI-C5 XomeTox project funded by CEFIC. Therefore male Wistar rats were exposed to a direct (6-propyl-2-thiouracil, PTU) and an indirect (phenytoin) thyroid toxicant (BASF), and proteomics was applied to thyroids and livers. Thereby two doses were tested for each drug and the samples were analyzed at three time points, including one after a recovery phase.

Based on the obtained data, significant changes compared to untreated controls were investigated for the different conditions, with subsequent KEGG enrichment analyses based on the significantly altered proteins (SAPs). Thus, we found that the use of phenytoin did not affect the thyroid as indicated by the lack of significant changes, while slight changes (up to 82 SAPs) were observable in the liver. These proteins were related to KEGG pathways like chemical carcinogenesis, glutathione, and xenobiotics metabolism via cytochrome P450. Notably, after the recovery period, no significant changes were observable anymore, suggesting full rehabilitation. Also, after treatment with PTU, only slight effects were induced in the liver even with the higher dose, including effects on carbon and amino acids metabolism, which were ameliorated after the recovery phase again. In contrast, such a full recovery was only achieved for the lower dose in thyroid and not for the higher dose, which led to stable effects on carbon metabolism, oxidative phosphorylation, and lysosomal processes was still enriched after the recovery time. These results indicate that the PTU effects on the thyroid were more severe than those on the liver.

Additionally, a Weighted Gene Correlation Network Analysis was applied to identify key drivers, which are supposedly valuable biomarker candidates. Thereby P450 family members such as CYP2B1 and CYP2C70, which are involved in hepatic metabolism and detoxification, were found significantly connected with the drug-induced liver toxicity. ATP5FA (mitochondrial ATP synthase subunit alpha) was identified in thyroid, which is significantly activated and associated with drug type and dose.

In summary, this study allowed mechanistic insights into direct and indirect DITT, and the identification of biomarker candidates, thus potentially facilitating future risk assessment of novel drugs.

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