Mechanistic comprehension of the impact of exposures calls for techniques that convert ever-increasing literature-based scientific knowledge into a format that is suitable for modelling, reasoning, and data interpretation [1-3]. The Biological Expression Language Information Extraction workflow (BELIEF) facilitates the transformation of unstructured information described in the literature into structured knowledge [4]. Through the BELIEF platform, we were able to create a network model that captures significant mechanisms in the context of Liver Xenobiotic Metabolism into the Biological Expression Language (BEL). Liver is a critical organ responsible for the elimination of toxic compounds by converting them into suitable forms during the Xenobiotic Metabolism process [5, 6]. Nuclear receptors and transcription factors play a pivotal role in this comprehensive network model. This network model includes the signaling pathways that lead to the activation of enzymes responsible for the three phases of Xenobiotic Metabolism: Phase I in which lipophilic chemical compounds are converted into their hydrophilic forms. Phase II, responsible for processes such as glucuronidation, sulfation, methylation, and acetylation, and Phase III, responsible for the elimination of xenobiotic metabolites through specific membrane transporters.

The Xenobiotic Metabolism Network Model

The selected original articles were compiled into three different networks models representing the Phase I, Phase II and Phase III mechanisms which take place during the Xenobiotic Metabolism.

In the context of Xenobiotic Metabolism, networks model represented by Phase I, Phase II and Phase III mechanisms were merged. This resulted in a network with 1386 edges and 446 nodes. Nr1b2, Nr1d2, Ahrr, and Nr1d1 are the most connected nodes strongly represented in all phases of Xenobiotic metabolism network model (represented in circular yellow shape). This indicates that these common nodes play an important role in all phases involved in the Xenobiotic Metabolism network model. Comparative analysis on the networks models strongly reveal that the most connected nodes in the Phase I network model are represented by Cbtl1, "PPP1R Family" and "PPP2R Subunit A Family" Cyp2a5, Prkaa1 (represented in circular red shape), whereas, Klf1, Itm2a, MAPK1 and Upg1b9 are the most connected nodes in Phase II (represented in circular blue shape) and Abcc2, Abcc9, Nr1f2, Thr, Thr, Abcc5 are highly connected in Phase III (represented in circular green shape). This indicates that these specific nodes play an important role in the Xenobiotic metabolism network model.

Conclusions

This causal biological network model developed with the BELIEF workflow may support efforts to elucidate new mechanisms involved in the Xenobiotic Metabolism [7]. The network model analysis highlights that common nodes such as Nr1b2, Prxra, Ntr22, Ahr and Nr12 drive all three phases of Xenobiotic Metabolism. These common nodes are for the most of them nuclear receptor family members and it shows that nuclear receptors are fundamental players in the Xenobiotic Metabolism. Most importantly, the network model analysis highlights the strategic role of specific regulatory factors (such as Chnmt, Kcnp1 or Abcc2) that are only involved in the specific phase of the Xenobiotic Metabolism as demonstrated with the activation of bile excretion transporters such as Abcc2 and Abcc9 in the Phase III of Xenobiotic Metabolism.

References


The Xenobiotic Metabolism Network Model Analysis

The nodes of the networks correspond to biological entities (e.g., protein abundances, activities, and biological processes).