In silico prediction of xenobiotic metabolism in humans

Fangping Mu[1]

***Short Abstract* — Xenobiotic metabolism in humans is catalyzed by a few enzymes with broad substrate specificities, which provide the overall broad chemical specificity for nearly all xenobiotics that human encounter. Xenobiotic metabolism are classified into functional group biotransformations. Based on bona fide reactions and negative examples for each reaction class, support vector machine (SVM) classifiers are built. The input to SVM is a set of atomic and molecular features to define the electrostatic, steric, energetic, geometrical and topological environment of the atoms in the reaction center under the molecule. Results show that the overall sensitivity and specificity of classifiers is around 87%.**

I. Purpose

BIOTRANSFORMATION is the process whereby a substance, usually a foreign compound (xenobiotic), is chemically transformed in the body to form a metabolite or a variety of metabolites. Chemical transformations can activate a xenobiotic rendering it toxic, or can alter a xenobiotic to a non-toxic species. The metabolism of xenobiotics is divided into phase-I and phase-II reactions, which sometimes, but not always, occur sequentially. Xenobiotic metabolism is accomplished by a limited number of enzymes that exhibit broad substrate specificities. These enzymes conduct limited types of biotransformations. The majority of Phase-I reactions occur via oxidation, including aromatic and alphatic hydroxylation, N- and O-dealkylation, deamination, and nitrogen and sulfur oxidations. Phase-I reduction reactions include nitro reductions to amines and dehalogenation, as well as the major hydrolysis reactions of esters and epoxides. In phase-II glucuronidation and sulfation are the major biotransformations. Other Phase-II reactions include acetylation, amino acid conjugation, glutathione conjugation, and methylation.

Expert systems represent the state-of-the-art xenobiotics metabolism prediction systems. These systems are rule-based systems designed to identify functional group transformations that occur in known reactions and then by generalizing, to formulate reaction rules for global application. These rules can provide reasonable prediction of all possible metabolite formation. However, they commonly predict many more metabolites than that are observed experimentally. Ranking the possibility of metabolite formation is still not consistently available.

To overcome the significant number of false-positives in rule-based systems for metabolism prediction, we investigated machine-learning technology for xenobiotics metabolism prediction (Mu et al., 2006).. We collected human xenobiotic reactions from MDL's Metabolite database and classified reactions according to rules based on functional group biotransformations. For each reaction rule, the reaction center can be well defined, and is represented as a molecular substructure pattern using SMARTs, which is a language for describing molecular patterns. Using the SMARTS patterns, we identified potential reaction centers for each reaction class using the identified metabolites in MDL's Metabolite database. Each set of potential reaction centers was divided into negative and positive examples. More than 54 atomic properties were used to model the topological, geometrical, electronic and steric environment of the atoms in the molecule, and more than 81 molecular properties were used to model the shape, surface, energy, and charge distribution of the molecule and Support Vector Machines were used to separate the positive and negative examples for each reaction class. Totally 36 biotransformations have been modeled. Results show that the overall sensitivity and specificity of classifiers is around 87%.

To demonstrate the relevance of metabolism to toxicity, we used epoxide hydrolysis as an example. Totally 489 chemicals with epoxide moieties are collected from Toxnet (http://toxnet.nlm.nih.gov/), and majority of them are stable epoxides. Using the metabolism prediction model for epoxide hydrolyzation, only 24, or 4.9%, are predicted to be hydrolyzed enzymatically.

II. Conclusion

Global classification models are proposed to predict the fate of xenobiotics in humans. The methods represent a step toward the development of computational tools that can predict xenobiotic metabolism pathways in humans.

References

[1] Mu F, Unkefer PJ, Unkefer CJ and Hlavacek WS (2006) Prediction of oxidoreductase-catalyzed reactions based on atomic properties of metabolites. *Bioinformatics* **22:**3082-3088.

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[1]Theoretical Biology and Biophysics Group, Theoretical Division, Los Alamos National Laboratory, Los Alamos, NM 87545, USA. E-mail: fmu@lanl.gov