Novel Metabolic Descriptor Based on Xenobiotic Induced Cytochrome P450 Transcription for Carcinogenicity Prediction

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INTRODUCTION

Cytochrome P450 (CYP) enzymes play an important role in xenobiotic metabolism. They can help in detoxification by elimination of potential carcinogens, or facilitate toxicity by conversion of primary non-carcinogens (procarcinogens) into secondary carcinogenic metabolites.

Cytochrome P450 enzymes are either expressed constitutively or induced by certain substrates. Induction is usually a protective mechanism and helps in detoxification, but it can also lead to increase in production of carcinogenic metabolites.

CYP enzymes are subdivided into various families based on the percentage of amino acid sequence identity. The major CYP families are CYP1 (CYP1A,1B), CYP2 (CYP2A-E), and CYP3.

CYP2D6, CYP3A4, CYP2C9, CYP2C19 and CYP1A2 have been found to be involved in ~75-90% metabolic reactions. CYP2D6 alone is involved in the metabolism of ~70% marketed drugs.

METHODS

In-vitro Assay Data

- CellzDirect CYP1A1, CellzDirect CYP1A2, CellzDirect CYP3A4 data was obtained from ToxCastDB
- The assays report change in expression of the enzymes in an in-vitro test after exposure for 6, 24, and 48 hrs

Carcinogenicity data

Obtained from publically available carcinogenic potency database (CPDB) and chemical carcinogenesis research information system (CCRIS)

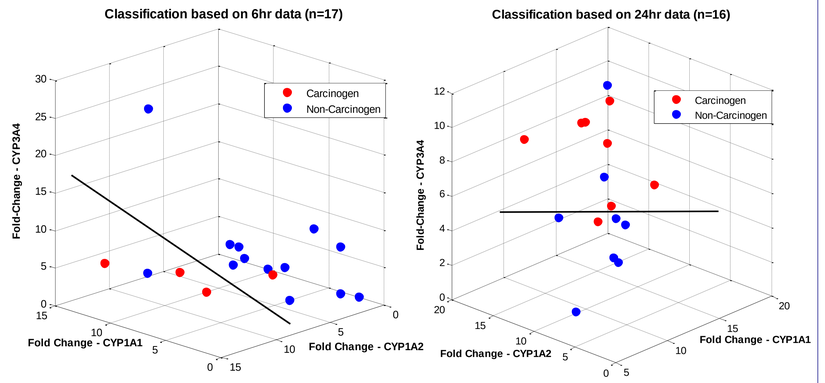
Support Vector Machines (SVM)

- A supervised machine learning algorithm used in classification and regression analysis
- Linear binary classifier which calculates an optimal hyperplane for categorizing new data

Leave One Out Cross Validation

- *N* experiments performed with (*N-1*) training chemicals and *1* test chemical
- Model is tested for classification on the one left out test chemical

RESULTS



MOTIVATION

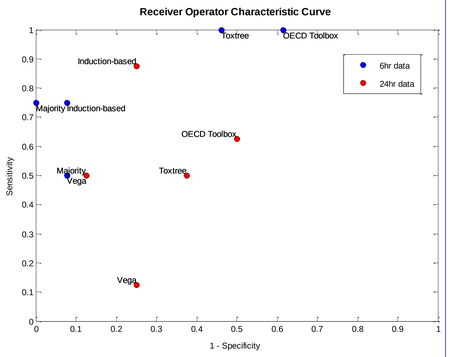
CYP1A1, CYP1A2, CYP2E1 and CYP3A4 enzymes are found to be involved in the metabolism of procarcinogens.

Literature supports specific relation of cytochrome P450s to carcinogenicity:

- **CYP1A1**, **CYP1B1** and **CYP2E1** have been found to play specific roles in carcinogenesis[1]
- **CYP1B1**, **CYP1A** and **CYP2E** have been found to be induced in tumor tissue[2,3]

RESULTS

Metrics \ Model	Induction based classfier	Toxtree	Vega	OECD Toolbox	Majority
6hr (n=17)					
Accuracy(%)	88.2	64.7	82.4	52.9	94.4
Sensitivity(%)	75.0	100.0	50.0	100.0	75.0
Specificity(%)	92.3	53.9	92.3	38.5	100.0
24hr (n=16)					
Accuracy(%)	81.3	56.3	43.8	62.5	68.8
Sensitivity(%)	87.5	50.0	12.5	62.5	50.0
Specificity(%)	75.0	62.5	75.0	50.0	87.5



CONCLUSION

- The SVM based classification results strongly suggest a correlation between the carcinogenic potential and the ability of test chemicals to induce transcription of CYP1A1, CYP1A2 and CYP3A4 enzymes
- The ROC curve demonstrates a better trade-off between sensitivity and specificity by using the induction-based classifier method versus several *in silico* tools
- The results demonstrate that xenobiotic induced cytochrome P450 expression data can be used as a metabolic descriptor in QSAR studies for carcinogenicity prediction

FUTURE WORK

- Obtain more induction data for further understanding of the role of carcinogen/procarcinogen in induction of various CYP450s
- Develop methods to incorporate change in expression of CYP enzymes as a descriptor in QSAR modeling for carcinogenicity prediction
- Investigation of the role of CYP450s in carcinogen/procarcinogen metabolism

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