Elucidation of Xenobiotic Responsive and NR Mediated Pathways/Networks

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1 Introduction

The so called drug-metabolizing enzymes (DME), which are classified into phase I, phase II, and phase III enzymes, biotransform and subsequently transport not only drugs but also xenobiotic chemicals, some nutrients and even some endobiotics. These are now considered as the “processor” part of the biological organisms’ adaptive defense sensor-processor system for xenobiotic chemicals. It is relatively recent that nuclear receptors were identified as the main sensors in this defense mechanism, for two members of the nuclear receptor superfamily, the pregnate X receptor (PXR) and the constitutive androstane receptor (CAR), were discovered to induce important drug-metabolizing enzymes. We have started to elucidate the overall pathways and networks in these sensor-processor systems. Our eventual goal is to develop a database, but data and knowledge available at present is far from comprehensive for this purpose. Thus in this presentation we discuss the design concept, component systems, and some preliminary findings.

2 The Sensor-Processor System Model

We take three classes of protein families, the aryl hydrocarbon receptor (AhR), nuclear receptors, and the nuclear factor-E2 p45-related factor 2 (Nrf2), as the basic sensors. All of these protein families are transcription factors activated directly (in case of AhR and nuclear receptors) or indirectly (in case of Nrf2) by incoming ligands such as xenobiotic chemicals or drugs. In case of AhR and nuclear receptors the ligand-activated receptor forms a dimer, either homo-dimer or hetero-dimer, that subsequently binds to the specific DNA sequence region called the response element (RE). This binding recruits cofactors (co-repressors or co-activators), and trigger synthesis of messenger RNAs (mRNAs). The product proteins from these mRNAs include enzymes that either biotransform the incoming chemicals or transporting them or their metabolites. In case of Nrf2 the pathways for binding to the DNA sequence, the antioxidant response element (ARE)/electrophile response element (EpRE), are much more complicated. However basic scheme (Figure 1) can be applicable with slight modifications.

3 Data Collection and Organization

We focused our attention mainly on humans. Primary data and knowledge were mostly collected from literature (1), and were analyzed and annotated manually. Subsequently additional data were collected from wide range of relevant databases in the public, some of which such as K/Bank were developed by the authors (2). These data and knowledge were organized into component files in table like forms based on
Figure 1: Sensor-Processor Model of Xenobiotic Responsive System

binary relations. They cover the data and knowledge on ligand-receptor (transcription factor) relations, ligand-activated receptor dimers, cofactors, dimer-cofactor complex, dimer-DNA response element combinations, dimer-cofactor-DNA response element complex, target genes, binding sites of target genes (promoter structures), disposition enzymes (product of target genes), disposition enzyme-substrate relations. Genetic variation data were also added to these component files. All of these files were compiled in EXCEL, were combined to databases using ACCESS.

4 Results and Discussion

Connecting the component data files (tables) one can deduce logical relations among nuclear receptors and their target genes. The resultant pathways and networks are considered as gene regulatory networks. We have identified several “network motifs” such as auto regulation, reciprocal regulation, and chain reactions. Two most difficult problems in our elucidation are identification of cis-regulatory elements and entire target genes. Right now new experimental methods such as microarray analysis, chromatin immunoprecipitation (ChIP) method, and/or RNAi have been recruited to these problems. Computational approaches have also been proposed. However it is now well admitted that neither experimental nor computational approach alone can accomplish the goal, and combinatorial approach is necessary. Our research is relevant to integrate these experimental and computational results to refine the sensor-processor system models and produce a comprehensive database (3) for xenobiotics and drug disposition.

References

