Tracing Back Xenobiotic Responsive and NR Mediated Pathways/Networks

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1 Introduction

Nuclear receptors (NRs) are transcription factors that form a superfamily that share common protein organization. To date, NRs are exclusively found in animals and sponges, which has led to the notion that they arose in this animal kingdom, Metazoa. It is now widely accepted that NRs are taking balance of materials and energy in these organisms. NRs are playing the role of sensors while their target gene products play the role of processors of the incoming xenobiotics and endobiotics. Important and well studied these processors are so called drug-metabolizing enzymes (DME), which are classified into phase I, phase II, and phase III enzymes. Two members of NRs, the pregnane X receptor (PXR) and the constitutive androstane receptor (CAR), were discovered to induce some of these drug-metabolizing enzymes. We have started to elucidate the over all pathways and networks in these sensor-processor systems [1]. Though our eventual goal is to develop a database, the data and knowledge available to date is far from comprehensive for this purpose. In this presentation we focus our attention on evolutional aspect of these systems.

2 The Framework Model

From material processing view points three classes of protein families, the aryl hydrocarbon receptor (AhR), nuclear receptors, and the nuclear factor-E2 p45-related factor 2 (Nrf2), seem to play the role of 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 triggers 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. These sensor-processor systems also play important roles for taking energy balancing, for energy are always embodied with materials. However there are few additional transcription factors that work closely with NRs for energy expenditure. Particularly important members of the latter are C/EBPs and SREBPs. The basic framework of the molecular processing is shown in Figure 1.

3 Evolutional Feature of Nuclear Receptors

Completion of the human genome projects and its successive sequencing efforts on wide range of eukaryote organisms greatly enforced comparative genomic studies of NRs. It was now found 48 NR members in human, 49 in mouse, 47 in rat, 18 in Drosophila, 68 in fugu, and more than 270 in C.elegans. However interesting comparison beyond the number of NRs is how ligands to NRs relate to the processors, i.e., drug metabolic enzymes. From the evolutilional viewpoint several questions have raised on NRs. For example some NRs are still considered to be orphan, and a question is raised on the ancestor NRs that whether they are orphan or not. Another question is how NRs are formed from uni-cellular organisms to that of multi-cellular animals. How the sensor-processor relations are conserved or evolved (changed) during these evolutions. Are there any traces of NRs in uni-cellular organisms? If so what are their relation to metazoan NRs? Plants and animas share many drug-metabolizing enzymes. Then what are the evolutional differences
of the relation between sensor and processor genes between animals and plants? Already there exists studies towards for answering these questions [2]-[4].

We are particularly interested in the problem of searching NRs ancestors in uni-cellular organisms and plants. For studying uni-cellular organisms we chose yeast (Saccharomyces cervisiae) as the model and looked for proteins homologous to NRs.

![Sensor-Processor Model of Xenobiotic/Endobiotic Responsive System](image)

**Figure 1: Sensor-Processor Model of Xenobiotic/Endobiotic Responsive System**

### 4 Results and Discussion

We have scanned Genome Threading Database and found a protein whose 3D structure has some sites similar to known the ligand binding domain of a NR [5].

Our research may be relevant to multidrug resistance problem in cancer, for this phenomenon is explained by function of some transporters [6].

### References


