Pathways/Networks to Syndrome X

Tsuguchika Kaminuma[1]
kaminuma@cbi.or.jp
Masumi Yukawa[2]
yukawa@cbi.or.jp
Naomi Komiyama[2]
komiyama@cbi.or.jp
Kotoko Nakata[3]
nakata@nihs.go.jp
Hiroki Momose[4]
momocom@tmd.ac.jp
Yoshitomo Tanaka[4]
ytanaka@bioinfo.tmd.ac.jp
Hiroshi Tanaka[4]
tanaka@cim.tmd.ac.jp

[1] Biodynamics Inc.
[2] Chem-Bio Informatics Society
[3] National Institute of Health Sciences
[4] Medical Research Institute, Tokyo Medical and Dental University

Keywords: nuclear receptors, pathways/networks, SyndromeX

1 Introduction

Nuclear receptors form a superfamily of proteins that function as ligand-activated transcription factors. They were first discovered as endocrine hormonal receptors, but later orphan nuclear receptors that function as metabolic and toxicological sensors were found. Thus the nuclear receptors are found out to be important for the endocrine system and its disorders, health effect of environmental chemical pollutants, drug discovery, and wide range of metabolic health disorders, which are collectively called Syndrome X. Under the name of the Nuclear Receptor and Syndrome X (NR-SX) Project we are developing the knowledge environment for the nuclear receptors and metabolic disorders. Our efforts are focused on the pathways and networks that are essential for Syndrome X.

2 Method

The nuclear receptors and Syndrome X offer wide range of chemical computing and bioinformatics research topics. To name but a few; protein modeling, ligand-receptor docking, interaction of DNA and receptor dimer complex, identification of target genes and cis-regulatory elements, building pathways and networks consists of ligands, nuclear receptors, their target genes, their product proteins, modeling and simulation of the pancreatic beta-cell, adipocyte, insulin signaling, and obesity. The core of chemical computing is molecular modeling and docking study, while the core of bioinformatics is the pathways and networks containing nuclear receptors as their nodes. We set our primary goal to develop a simple but coordinated nuclear receptor database from which pathways and networks can be elucidated.

The database called the "core database" contains ligands, receptors, dimerization partners, ligand-activated receptor complexes, cofactors, DNA response elements, target genes and their product proteins, and their functions. These data are searched from the public databases on the Internet or from literatures. Computational methods have been developed to identify target genes and their cis-regulatory (response) elements. The core database is implemented using ACCESS. References are put in a separate file management system. Pathways and networks are presented in ad hoc descriptive systems. All of these products are eventually put on a website for public access.

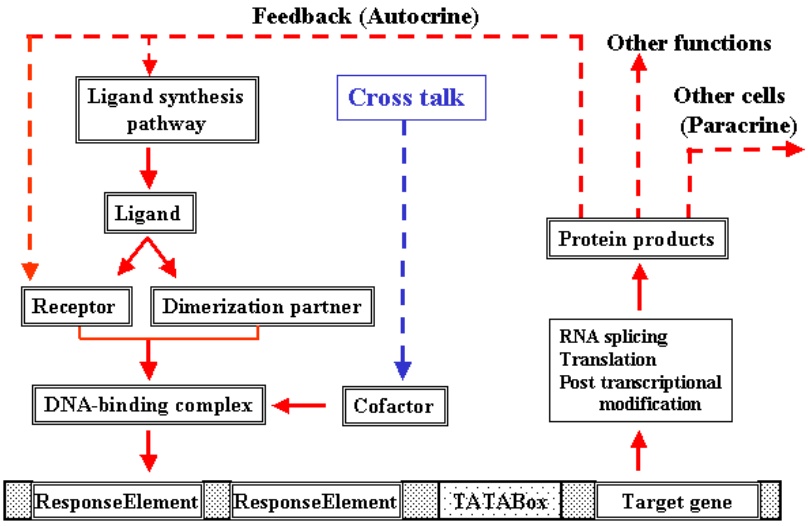

Figure 1:

3 Results

3.1 Implementation

There already exist various nuclear receptor databases in the public domain that contain classification, nomenclatures, gene and amino acid sequence structures, gene loci on the chromosomes, and three dimensional structure data of ligand binding domains and DNA-binding domains. The website that has links to these public databases is implemented on the Chem-Bio Informatics web server. The prototype core database, the reference file system, and descriptive pathways and databases were implemented on a separate Windows PC.

3.2 Application

3.2.1 Target Gene Search

The response element to which ligand-binded receptor dimer binds is a part of the promoter region of the target genes of the nuclear receptors. Although a large number of genes are identified as the target genes of nuclear receptors, experimental efforts are continued to find complete list of such genes. Pure computational approach to identifying the target genes and their response elements are impossible, and knowledge-based approach combined with algorithmic approach is a practical solution. The core databases are useful for such problem.

3.2.2 Drug-Drug Interaction

The target genes of nuclear receptors, particularly PXR and CAR, include genes for drug and xenobiotic metabolizing enzymes (cytochromes P-450, CYPs) and transporters. Thus core database has links to the latter databases in the public. These information are important not only for drug-drug interaction, but also for drug-food, or drug-xenobiotic chemical interaction.

3.2.3 Modeling Syndrome X Disorders

Syndrome X or "metabolic syndrome X" refers to a group of health disorders that includes overweight (obesity), insulin resistance (type 2 diabetes), abnormal blood fats (hyperlipidemia), high blood pressure (hypertension), and atherosclerosis. Because they are metabolic disorders, it is suspected that they share the common key molecular players such as insulin, leptin, free fatty acids, or resistin. Based on the knowledge accumulated in the core database we are developing pathways/networks cell models for pancreatic beta cell and adipose cell, and inter-organic signal communication such as insulin signaling.

References

[1] Kaminuma, T., Pathways and networks of nuclear receptors and modeling, *Chem-Bio Informatics Journal*, 3(3):130–156, 2003. (`http://www.cbi.or.jp/cbi/CBIj/vol3/3_130-E.pdf`)