

Analysis of Gene Regulation Network by Nuclear Receptor PPAR

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1 Introduction

Peroxisome proliferator-activated receptor (PPAR) is a member of orphan nuclear receptors. It is the ligand-activated transcription factor that controls the lipid metabolism and is now studied from etiology viewpoint of obesity and type 2 diabetes. A large number of genes have already been identified as target genes activated or repressed by the receptor, experimental efforts are continued to find complete list of such genes. This subject is related to identification of regulatory region of arbitrary gene or binding site of transcription factors, therefore informatics approach is expected. Since a pure computational approach in identifying the target genes and cis-regulatory (response) elements is currently impossible, knowledge-based approach combined with algorithmic approach is a practical solution. We have tried to elucidate PPAR target genes by the both approaches and analyze the pathway/network consisted of ligands, target genes and their product proteins.

2 Method

Three PPAR isoforms have been identified so far, and they are different to each others in the ligand specificity and the expression tissues. We made a list consisted of ligands corresponding to each isoform (alpha, beta/delta, gamma), response elements, cofactors and target genes including candidates. These data are searched from the public databases on the Internet or from literatures. Furthermore to search for other target genes, a new algorithm was developed so that it can identify response elements, target gene loci and their neighbor genes on the chromosomes by using databases.

3 Results and Discussion

We identified 67 genes that were related to gene regulation by PPAR as the result of making the list. However, sequences of response element were considerably different. Fig. 1 shows the frequency of nucleotides appearance at each position made from 43 response elements whose sequences were known. We then tested the algorithm based on the frequency.

When gene regulatory networks including ligands, target genes and their product proteins were analyzed by the results of above two approaches, we revealed pathway/network which was consisted of other nuclear receptors, target genes and interactions with pathways from cell surface receptor. However it will be necessary to consider species differences in availability of response elements because there is a case that a response element in human gene is functional but in rat gene is not.

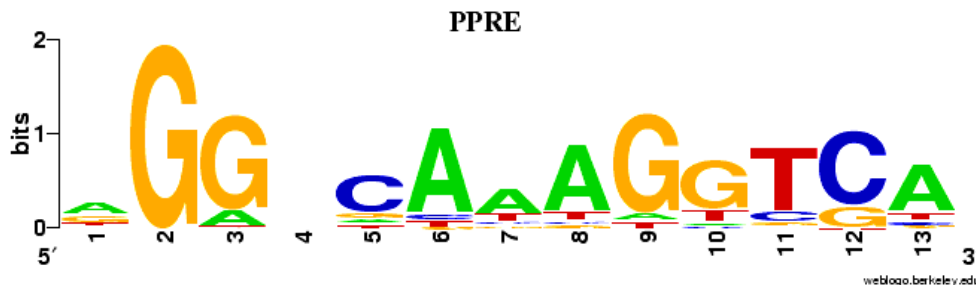


Figure 1: The frequency of nucleotides appearance at each position made from known 43 PPAR response elements (PPRE). This image was made with “WebLogo”. See also ref.[6].

4 Application

Obesity and type 2 diabetes are deeply interrelated to each other because they are metabolic disorders. Fat and glucose derived from exogeneous nutrients are key molecules. Since PPAR involved in energy metabolism, Pathways/Networks via PPAR would be valuable for understanding of these mechanisms. To explain the function of another key molecule insulin on signal transductions we are developing pathways/networks cell model for pancreatic beta cell based on the result.

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