

The Functional Flow of Drug Target Protein in Metabolic Pathway

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Abstract

Drug discovery is essential project and research area in pharmaceutical industry. Identification of drug target protein is first and one of most important step in drug discovery although it is usually high risk and expensive process. In this paper, we analyze the functional flow of drug target protein and related neighbored protein of them in metabolic pathway. Because most of drugs have to affect one or more than two metabolic pathway in positively or negatively, we need to study about side effects of new drug in long term. Thus, this study is helpful to identify drug target protein which is minimize the side effects if we can characterize the functional flow of drug target protein and related neighbor protein in metabolic pathway. The prediction accuracy is 73%(sensitivity: 79%, specificity:69%).

Keywords: drug target protein, functional flow, metabolic pathway

1 Introduction

Drug discovery is essential project and research area in pharmaceutical industry, and many companies spent immense efforts and cost to discover new drug. Drug target protein is a protein which is affected by specific drug or toxic chemicals. Since drug must have strong effects on a specific metabolic pathway and minimally interfere in all the other normal metabolic pathways, the identification of undesirable secondary effects (side effects) is main challenge and research issue in area of developing new drugs [1]. Although there are several bioinformatics tools that have opened for new ways in drug discovery, most of drug discovery processes seem not to be performed by a well-defined logical process, but by a very accidental and fortuitous process. Currently, approved drug target protein list is opened to public in DrugBank[2].

In this paper, we focused on the effects of drug target proteins and its interactions in metabolic pathways rather than just attribute of drug target protein itself. For predicting new drug target protein, the functional flow model is suggested which relation between protein's function. The prediction accuracy is 73%(sensitivity: 79%, specificity: 69%). Thus, this study is helpful to identify drug target protein and reduce money and cost to develop new drug.

2 Method and Results

2.1 Data and materials

For analyzing functional flow of drug target proteins and related neighbor proteins in metabolic pathway, we prepared data sets from DrugBank[2] and KEGG[3] databases. The functional information of proteins which is molecular function information defined in GO(Gene Ontology) is used for creating functional flow. KEGG provide metabolic pathway information. The signal transduction and other disease related pathways is used, because other metabolic pathways are more related with enzyme and not specialized for human. The relationship and directions between nodes in pathways are important key aspects, thus we use them with GO functional information.

2.2 Method

The Functional Flow Model is used for predicting new drug target protein. This model consist of protein's molecular function, which is defined by GO, and the interaction or relation in metabolic pathway, and assign direction.

2.2.1 Creation Functional Flow

- Find drug target protein in metabolic pathway
- Make a node with function of target protein

- Make a node with function target protein's neighbor protein
 - Make a edge with relation between target and neighbor protein
 - Assign weight which frequency
- 2.2.2 Prediction new drug target protein using functional flow
- Bring target metabolic pathway
 - Make function pair of each protein and neighbor protein in metabolic pathway
 - Calculate score which the sum of each edge's weight
 - The highest score protein is high possible new drug target protein in target pathway

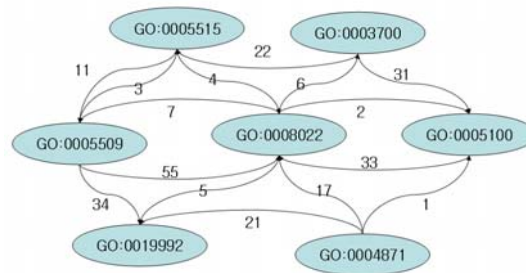


Figure 1. example of functional flow

2.3 Results.

Figure 2 shows the functional flow of drug target proteins and related neighbor proteins. Each table shows the frequency of molecular functions of proteins which defined in GO and the frequency of relation types between proteins. In addition, it shows the drug target and neighbor protein in metabolic pathway has characteristic function.

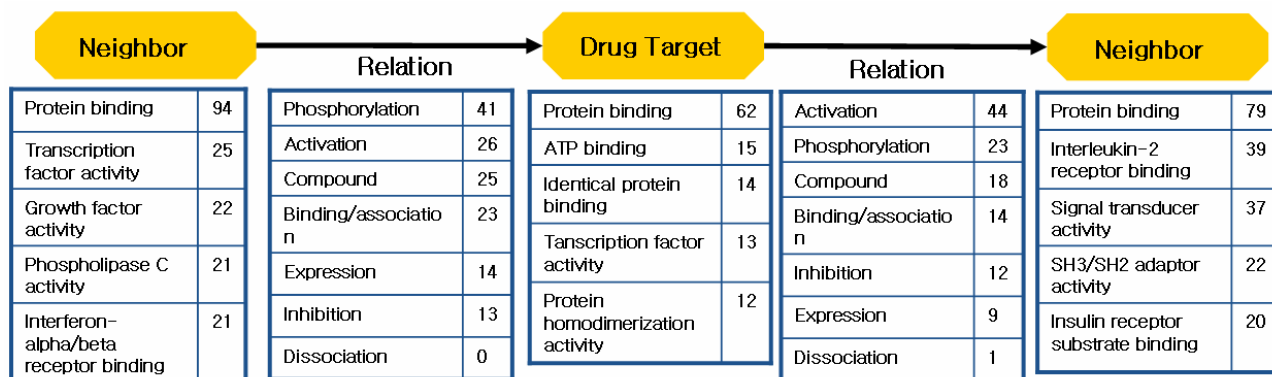


Figure 2. The functional flow of drug target proteins and related neighbor proteins.

The evaluation of functional flow is 73% accuracy. For evaluation, a 20% of metabolic pathway which has drug target proteins is used to calculate sensitivity, and other non-drug target is used to calculate specificity. Therefore, sensitivity is 79%, and specificity is 69%.

3 Discussions

As illustrated in Figure 1, the functional in-flows and out-flow are distinguished between drug target proteins and neighbor proteins. Although GO functional information is not enough to explain explicit biological meaning, we expect that our approach help to identify new drug target proteins. Since our suggested functional flows are based on approved drug target proteins which have minimum side effect, we can predict candidates of drug target proteins based on their functional flows and interactions. Therefore, researcher can avoid unnecessary experiments for discovering new drug target proteins, and they can save time and cost.

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