Systematic Identification of differential expression networks in chemosensitive and chemoresistant ovarian cancer

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1 Introduction

Chemotherapy resistance in ovarian cancer is related to multiple factors, and assessment of these factors is necessary for the development of new drugs and therapeutic regimens. One of the factors is the different reactions in biological interaction networks that cause chemoresistant. In other words, the mechanisms and related biological interconnectivities that contribute to chemotherapy resistance are relatively unknown. Therefore, this work aims to provide a system to identify the differential expression networks associated with drug response in chemosensitive and chemoresistant ovarian cancer. This work have three major objectives, (i) to explore differential expression networks or novel predicted genes that are involved in chemoresistant mechanism, (ii) how these genes interact with each other, and (iii) to analysis differential expression networks between chemosensitive and chemoresistant response.

2 Method and Results

2.1 System Overview

A system flow diagram of the corresponding processes is shown in Figure 1. The system is composed of heterogeneous biological databases integration, seed nodes selection, network identification, scoring and filtering, and differential expression networks analysis. In order to construct the large biological network, we collect pathways from public databases such as Pathway Interaction Database [1] and KEGG [2]. We perform a systematic screen for transcription factors (TFs) involved in the DNA damage response as well. The information of TFs is extracted from TRANSFAC [3] database. TFs will be selected according to any one of two criteria; one is TFs that are annotated by DNA damage or DNA repair related GO terms [4]. The other criteria is that TFs are 2-fold differentially expressed after drug treatment.

Next we input seed nodes to identify sub-networks from the large biological network and perform sub-network scoring and filtering by ovarian cancer expression values [5]. By mathematical means, this procedure extracts a sub-network from the large biological network that is spanned by the seed nodes. We use genes, proteins and other cellular components coded as nodes that are connected by edges in the identified sub-networks. Because the sub-network filtering step assumes weights on edges for scoring, and such edge weights must be calculated from gene expression levels. Thus, we transform the identified sub-networks into the line graph [6]. Then edges can be weighted by gene expression values directly. Following Ideker et al.[7], we analyze the gene expression data and to extract \(p\)-values for each expressed gene, and to calculate a total score of the sub-networks. Finally, we filter sub-networks according to calculated scores.

2.2 Results

Due to the limitation of pages, we only provide the Figure 2 to demonstrate one of the experimental results of identified network. The start and end nodes are IL1A and ADAMTS1, respectively. As shown in the diagram 2, several pathways are involved including MAPK signaling pathway, insulin signaling pathway,
and ErbB signaling pathway. In addition, Genes shown in Figure 2 represented by red circles indicate the connected nodes, that is, these genes connect two pathways. Connected nodes are key factors for joining two or more metabolic pathways or passing down signals. In this case, MAPK8 and GRB2 genes are connected genes. We also further analyze these genes by statistics method, betweeness and degree centrality of biological networks [8], and literature review to prove the performance of this system.

![Figure 1. The system flow diagram.](image1)

![Figure 2. One of the experimental results.](image2)

3 Discussions

We aim to provide a system to identify the differential expression networks associated with drug response in chemosensitive and chemoresistant ovarian cancer. The impact of these studies will be the identification of response networks that could present potential drug-targets for ovarian cancer. The major contributions of this approach are: (1) to reveal the phenomenon of chemoresistant mechanism and related interactions between genes by networks to emphasize the relationships of regulating or being regulated; (2) retrieving significant differential expressed gene sets from chemosensitive and chemoresistant expression data and crossing validation gene sets by calculating the values of betweenness and degree centrality in large complex networks; and (3) to provide new hypotheses of chemoresistant mechanisms by systems biology. In summary, differential expression network provides an excellent systems biology tool to identify and analyze systems level responses by a comparative approach. Differential network analysis not only offers insights into the mode of biological action of drug resistant but also provides information on potential key targets for further drug-development efforts.

References