Profiling the Nanoparticles Associated Metabolic Pathways

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Abstract

To explore the nanoparticles-dependent signaling pathways is a rapidly growing research field. Here, we globally elucidate the regulation modules of cellular molecules by using graph-based representation of complex networks. We have packed some useful bioinformatics methods (Matlab Simbiology and Pathway Studio) into an integrated system for graph-based representation and complex networks modeling. Here, this system is applied to the public literature and microarray database of nanoparticles and try to find out nanoparticles related genetic regulatory pathways. By comparing to different model organism system (bacteria, mice, cell line), we will establish a multidimensional (protein cellular location, time course expression pattern and chemicals interacting profiles) secondary database. The value added database will uncover some new relationships between genes and nanoparticles and provide useful information for the modeling of nanoparticles cellular regulatory pathway in an interactive form. The new modeling approaches should serve as a research platform to find protein candidates for nanoparticles associated diseases and provides a possible cue to improve the bio-chemo-informatics analyses on gene expression and molecular pharmacology.

1. Introduction

Biological pathway visualization has become a central theme of systems biological researches. Graph-based representation of complex networks can globally elucidate the regulation modules of cellular molecules [1]. By the use of graph-theoretical concepts and well-developed tools, one can predict the properties of the underlying interaction network and construct the working hypothesis of further experiments [2]. In this study, we attempted to construct a graph-based representation model for nanoparticles.

Bioinformatics systems biology is a cutting-edge biological field that focuses on high through-put experimental data mining, database organization, and the systematic study of complex interactions in cellular systems [2, 3]. Furthermore, the regulatory network or pathway modeling of cancer development processes becomes a major issue for bioinformatics systems biological studies in present day. Based on these bioinformatics studies, further lab-experiments can be conducted to clarify the pharmacologic potential and develop effective cancer therapies [3, 4].

Nanotechnology, a rapidly growing industry that manipulates materials and processes on a nanometer scale, open a world of creative possibilities. However, the nascent nanotechnology generates the potential adverse effects of nanoparticles on human health and the environment. Completed toxicological and mechanism of action information of nanoparticles is necessary for us to maximizing benefits and minimizing health risks [5, 6]. The possible toxicities of nanoparticles in cell culture and in mice have been investigated [7, 8]. Treatment of A375 human melanoma cells with the Nano-Se resulted in dose-dependent cell apoptosis as indicated by DNA cutting and phosphatidylserine translocation [8]. Organs from mice fed with nanoparticles showed nonspecific hemorrhage, lymphocytic infiltration, and medullary congestion [6, 9]. To model the potential toxicity of nanomaterials, more studies should be conducted on different model organism and under different routes of exposure with different forms of nanoparticles [9, 10].

There are only a few papers using microarray approach to study the nanoparticles-associated gene regulation [6-11]. Here, we are going to establish a more comprehensive secondary database which comparing different model system and data presented in a multidimensional from (protein cellular location, time course expression pattern and drug interacting profiles). The valued-added secondary database may suggest some new relationships between nanoparticles related genes and cellular process, and then we will model this cellular regulatory pathway in a novel electronic cell form by using Matlab toolbox. The new development should serve as a platform to find novel nanoparticles related cellular processes.

2. Methods

2.1. Omics Data Analyses of Nanoparticles

We use the Matlab Simbiology software to analyze nanoparticles (for example, quantum dots) microarrays from different sources. Matlab Simbiology is a well-developed data mining tool for the analysis of cDNA expression profiles. We thus calculate pair-wise correlations between gene expression and measures of nanoparticles susceptibility. A feature of consensus is identification of genes that cluster consistently with a master gene across approaches. The sensitivity of the metrics to the biases of the different clustering algorithms can be revealed by using simulated data [2, 4]. Furthermore, we also apply different algorithm such as relevance networks, phylogenetic type tree clustering, self-organizing maps by using Matlab-based toolbox in the redefinition of protein-protein interaction.

2.2. The Graph-based Representation and Model Construction

By use of the graph-based representation, it is possible for us to (i) analyze the literate about nanoparticles associated genes, (ii) analyze the gene expression patterns in different model organisms, and (iii) predict nanoparticles response based on toxicological gene expression profiles [1-3, 12].

3. Results

Pathway Studio is supplied with the ResNet Core database, which is a subset of RESNET 4.0 database. RESNET Core database contains canonical pathways and molecular interactions which have been compiled by manual citation and MedScan Information Extraction for well-documented molecular interactions [12]. The database includes a collection of more than 1,000 signaling pathways. A number of associations were found which are common for both pathological and pharmacological issues, such as cytokine production, differentiation, and protein secretion. Figure 1 showed that Quantum dots Cdse related biologically connective cascade. These substructures provide the common features in several pathways.

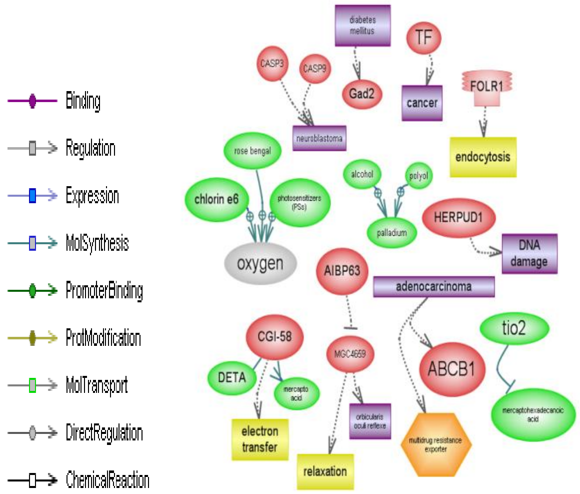

Fig. 1. PubMed Information Graph View of Cdse

Several studies suggested that quantum dots induce cell death via mechanisms involving both Cd2+ and ROS accompanied by lysosomal enlargement and intracellular redistribution [5-7]. Here, this model will build up by the expression profiles to demonstrate the potential role of quantum dots and its inhibitors in genetic regulation during cancer development [7, 9, 13].

Table 1. Discovered cellular processes associated with Nanoparticles

Process Type	Relation	Node
Binding	EGF ---- EGFR	2
Regulation	EGF ---> cancer	2
Regulation	breast cancer ---> ERBB2	2
Regulation	NTRK1 ---> differentiation	2
MolSynthesis	tio2 ---| mercaptohexadecanoic acid	2
MolTransport	MGC4659 ---> NQDs	2

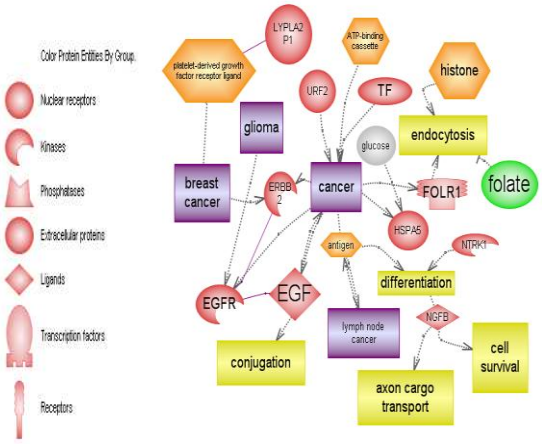

Figure 2. The directional graph associated with cancer

4. Conclusion

The application fields of nanoparticles range from medical imaging, new drug delivery technologies to various industrial products [6]. It is necessary for us to investigate the cytotoxicity and mechanism of action of nanoparticles before developing more new applications.

Several experimental results show that nanoparticles cytotoxicity can result from the generation of reactive oxygen species with the interplay of oxygen due to the strong affinity of the nanoparticles for the cell membrane. Further investigation on intracellular mechanisms found that nano-scale particles treatment triggered apoptotic cell death with the involvement of oxidative stress and mitochondrial dysfunction. [5-9].

In this study, we have presented an integrated approach for automatically finding nanoparticles regulatory modules in public literature and microarray database. In addition, our computational pipeline found dozens of other new nanoparticles related regulatory modules that constitute strong candidates for novel elements.

The novel methodologies development provides commanding analyses give a molecular explanation for the possible mechanism of gene-drug interactions. Future work will seek to strengthen this pipeline by improved exploitation of protein-protein interaction scoring system.

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