PhosNet: a web tool to reconstruct the protein kinase–substrate phosphorylation network integrated protein-protein interaction and biological pathway data

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Background and Motivations

Protein phosphorylation catalyzed by protein kinases is the most crucial post- translational modification and plays critical roles in signal transduction in eukaryotic cells. It has been estimated that one-third to one-half of all proteins in a eukaryotic cell are phosphorylated. The desire to explore the networks between protein kinases and substrates is motivated with the increasing number of experimental phosphorylation sites which has been identified by mass spectrometry-based proteomics. However, the phosphorylation network is not yet fully understood partly because the limited information of catalytic kinases. Manning *et al*. have identified 518 human kinase genes, which provide a starting point for a comprehensive analysis of protein phosphorylation networks. Thus, we aim to develop a novel tool, PhosNet, for reconstructing the protein kinase- substrate phosphorylation network by integrating experimentally verified

kinase-specific phosphorylation sites with information of protein-protein interactions (PPIs) and metabolic pathways.

Proposed Approaches

With an attempt to provide a full investigation of kinase-substrate phosphorylation network in human, a comprehensive dataset of experimentally validated kinase-specific phosphorylation sites has been integrated from dbPTM. Additionally, the information of protein-protein interactions and metabolic pathways are considered to reconstruct the intracellular signaling networks. This work has integrated a total of 19 PPI databases, including DIP, MINT, IntAct, HPRD, iRefIndex, UniProt, Spike, STRING, Reactome_Fls, Reactome, MolCon, MatrixDB, MPIDB, MINT, MBInfo, Interoporc, IntAct, InnateDB_IMEx, I2D_IMEx, DIP, BIND, BAR and APID.Up to now, there are more than 1900000 unique PPI data. Furthermore, we also collected the information of metabolic pathways from KEGG database. The integration of PPIs and metabolic pathways could provide a more comprehensive

In order to provide an interactive interface of phosphorylation networks for users, a public package of Java Script, Cytoscape, has been utilized in our web site. Users can submit a group of protein/gene names, the PhosNet efficiently returns an overview of protein phosphorylation networks associated with the submitted proteins/genes. Moreover, this work also integrated the gene expression data from 39 cancer series of GEO database. The expression profile of kinase and substrate genes in 39 cancers could be used to detect the potential biomarkers in a specific cancer.

Results and Conclusions

The PhosNet aims to provide a full investigation and interactive visualization of protein kinase-substrate phosphorylation network. Three major functions are provided on PhosNet web site: protein kinase-substrate phosphorylation networks, protein phosphorylation and

protein-protein interaction networks, as well as protein phosphorylation network and metabolic pathway. The PhosNet is now freely accessible via http://csb.cse.yzu.edu.tw/PhosNet/.