

Construction and Analysis of a Mammalian Kinase-Kinase Regulatory Network

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Kinases are enzymes that transfer phosphate groups to their substrates. They phosphorylate linear motifs on Serine, Threonine, or Tyrosine amino-acid residues. Phosphorylation regulates protein-protein interactions, protein translocation, protein degradation and protein enzymatic activity of kinase substrates. These events play vital roles in all cellular regulatory processes. The sequencing of the human genome identified 518 kinase genes. Since many protein kinases are substrates for other kinases and such relationships are known, we constructed a kinase-kinase mammalian regulatory network from data reporting kinase-substrate relationships from the literature. This network contains 385 kinases interconnected through 2156 links. Using the Markov Clustering and the Molecular Complex Detection Algorithms, we detected clusters of protein kinases in this network. Such clusters are subgraphs of densely interconnected kinases which may have specific functional regulatory roles. To associate function to clusters we performed statistical enrichment analysis of the kinase clusters against background datasets of lists of genes with a common associated function. We compared the kinase clusters against OMIM (Online Mendelian Inheritance in Man), GO (Gene Ontology), and protein domains from InterPro and PFAM to yield a better perspective of the kinome network by understanding the relationships between and within the kinase clusters.