World Academy of Science, Engineering and Technology
International Journal of Biotechnology and Bioengineering
Vol:8, No:06, 2014

Systematic Identification and Quantification of Substrate Specificity Determinants in Human Protein Kinases

Authors : Manuel A. Alonso-Tarajano, Roberto Mosca, Patrick Aloy

Abstract : Protein kinases participate in a myriad of cellular processes of major biomedical interest. The in vivo substrate specificity of these enzymes is a process determined by several factors, and despite several years of research on the topic, is still far from being totally understood. In the present work, we have quantified the contributions to the kinase substrate specificity of i) the phosphorylation sites and their surrounding residues in the sequence and of ii) the association of kinases to adaptor or scaffold proteins. We have used position-specific scoring matrices (PSSMs), to represent the stretches of sequences phosphorylated by 93 families of kinases. We have found negative correlations between the number of sequences from which a PSSM is generated and the statistical significance and the performance of that PSSM. Using a subset of 22 statistically significant PSSMs, we have identified specificity determinant residues (SDRs) for 86% of the corresponding kinase families. Our results suggest that different SDRs can function as positive or negative elements of substrate recognition by the different families of kinases. Additionally, we have found that human proteins with known function as adaptors or scaffolds (kAS) tend to interact with a significantly large fraction of the substrates of the kinases to which they associate. Based on this characteristic we have identified a set of 279 potential adaptors/scaffolds (pAS) for human kinases, which is enriched in Pfam domains and functional terms tightly related to the proposed function. Moreover, our results show that for 74.6% of the kinase– pAS association found, the pAS colocalize with the substrates of the kinases they are associated to. Finally, we have found evidence suggesting that the association of kinases to adaptors and scaffolds, may contribute significantly to diminish the in vivo substrate crossed- specificity of protein kinases. In general, our results indicate the relevance of several SDRs for both the positive and negative selection of phosphorylation sites by kinase families and also suggest that the association of kinases to pAS proteins may be an important factor for the localization of the enzymes with their set of substrates.

Keywords : kinase, phosphorylation, substrate specificity, adaptors, scaffolds, cellular colocalization
Conference Title : ICBCMB 2014 : International Conference on Bioinformatics and Computational Molecular Biology
Conference Location : Toronto, Canada
Conference Dates : June 16-17, 2014