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Charting the protein interaction landscape of human signaling systems

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Control of reversible protein phosphorylation by the interplay of protein kinases and phosphatases represents a key mechanism for the control of cellular processes in health and disease. It has been shown that complex formation with other proteins regulates localization, activity as well as substrate specificity of these enzymes and thus controls information processing via cellular signaling systems. We apply affinity purification and quantitative mass spectrometry (AP-MS) to systematically map the protein interaction landscape of human protein phosphorylation systems. Here report on inter lab reproducibility of systematic AP-MS analysis and discuss quantitative MS approaches for data filtering and the analysis of dynamic complex formation. We will present a comprehensive AP-MS study on the human CMGC kinase family, an evolutionary conserved group of 62 kinases, which include cyclin-dependent kinases (CDKs), mitogen-activated protein kinases (MAP kinases), glycogen synthase kinases (GSK), and CDK-like kinases. More than 80% of the 652 high confidence interactions we found represent novel interactions preferentially found in complexes of less studied CMGC family members. Besides modular organization and kinase family specific enrichment of functionally related proteins, the resolved kinase interaction data also showed a preference of CMGC kinase to form complexes with other kinases. Subsequent computational and experimental analysis demonstrates that AP-MS can be used to narrow down the kinase-substrate space at least for a subset of CMGC kinases. Finally, the resolved CMGC interactome revealed 132 interactions between kinases and proteins genetically linked to human pathologies. We thereby found a significant enrichment of cancer associated proteins and clustering of specific disease phenotypes within the interaction proteome of individual kinases.