with the first neighbors of the proteins. One of the manifestations of relation between two proteins is the co-expression pattern, therefore the network was integrated with co-expression profiles of interacting partners to achieve more robust and reliable protein interaction network. The reduced network has 2762 proteins and 9462 interactions, which was then characterized in terms of global topological properties such as degree distribution, clustering coefficient and betweenness. The network showed the scale-free network properties, following power law, with a degree exponent 2.70. Another implication of scale freeness is the high average clustering coefficient, 0.192, which is much more than the random network. This scale free behavior of the network allows the presence of hub proteins, which have central roles in the network. The accumulative degree and betweenness distribution of the network was encountered as the selection criteria for the identification of hub proteins. The resulting 15 hub proteins have an average of 69 interactions. The significantly enriched GO terms of these hub proteins suggested that these proteins have primary roles in signal transduction, regulation of cellular processes, biological regulation and cell communication.

doi:10.1016/j.nbt.2010.01.065

[P1.59]

A molecular systems biomedicine approach to Diabetes: characterization, prioritization and network analysis of new candidate genes from the apoptotic machinery

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Diabetes is a complex systemic disease, characterized by loss of pancreatic islet β cells and expansion of α cells. To gain a systems view on its etiology, we investigated the involvement of the apoptotic machinery (AM) through FACS, High-Throughput Real-Time RT-PCR, western analysis, and analyzed the modifications of AM transcriptome and AM protein nodes in two mouse pancreatic α and β cell lines (αTC1 and βTC1, respectively), after exposure to proinflammatory cytokines, for 24, 48, 72 h. AM genes markedly over or down expressed, and conserved between the mouse and *Homo sapiens*, were hypothesized to be causally involved in human Diabetes and ranked through functional (Fisher's inverse chi-square test) and protein–protein interaction (Wilcoxon matched-pairs signed-ranks test) prioritization methods. 34% of the 92 AM genes analyzed significantly varied their expression respect to controls. The increase in βTC1 cells of ATF3, BNIP3, NOS2, Ser20-p-P53, TNFRSF10B proapoptotic proteins and the decrease of antiapoptotic Tyr705-p-STAT3 suggest the involvement of both extrinsic and intrinsic apoptotic pathways. In αTC1 cells, neither the phosphorylated forms of P53 and STAT3 nor the death receptor TNFRSF10B changed their levels, whereas NOS2 was highly induced. Prioritization studies pinpointed *DDIT3* and *STAT3* as associated to Type 1 Diabetes, and *MAP3K14*, *NFKB1*, *NFKBIA*, *NFKBIB*, *NFKB2, RELA*, *STAT3* as associated to Type 2 Diabetes. Analysis of α and β cells regulatory networks showed that activation of P53 pathway and inactivation of STAT3 pathway play a crucial role in β cell death, while members of the NFκB complex and their regulators act as a common master module in both cell phenotypes. Our studies demonstrate the critical role of AM genes *DDIT3*, *MAP3K14*, *NFKB1*, *NFKBIA*, *NFKBIB*, *NFKB2*, *RELA*, *STAT3* in β cell death. We propose them as strong candidates for human Diabetes, as confirmed by the previous identification of *DDIT3*, *NFKB1*, *NFKB2*, *RELA* through epidemiologic and functional studies.

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doi:10.1016/j.nbt.2010.01.066

[P1.60]

Adding structural information to the von Hippel-Lindau (VHL) tumor suppressor interaction network

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The von Hippel-Lindau (VHL) tumor suppressor gene is a protein interaction hub, controlling numerous genes implicated in tumor progression. We focus on structural aspects of protein interactions for a list of 35 experimentally verified protein VHL (pVHL) interactors. Using structural information and computational analysis we have located three distinct interaction interfaces. lnterface B is the most versatile, recognizing a refined linear motif present in a number of otherwise non-related proteins. It has been possible to distinguish compatible and exclusive interactions by relating pVHL function to interaction interfaces and subcellular localization. A novel hypothesis is presented regarding the possible function of the N-terminus as an inhibitor of pVHL function.

doi:10.1016/j.nbt.2010.01.067

[P1.61]

Protein domain co-occurrences reveal functional changes of regulatory mechanisms during evolution

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The emergence of higher organisms was facilitated by a dramatic increase in the complexity of gene regulatory mechanism. This is achieved not only by addition of novel regulatory mechanism but also by expansion of existing mechanisms. Such an expansion