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Comparative Assessment of Large-Scale Maps of the Human Protein Interactome

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Short Abstract: We present here a first comparative assessment of different human protein-protein interaction networks. This analysis shows that the current maps have only a small, but nevertheless significant overlap. Furthermore, we detected intrinsic tendencies which are necessary to consider in future application of these maps.

Long Abstract:
Large-scale maps of protein interactions aim to constitute scaffolds for comprehensive models of complex molecular interactions within organisms. Recently, there have been a growing number of both experimental and computational efforts to systematically map the human protein interactome. A major task will be the integration of these distinct sources. However, previous studies of interaction maps in lower eukaryotes revealed a surprising divergence in interactions obtained for these model organisms. Thus, critical comparisons are necessary regarding the congruency of the different mapping approaches. We present here a first comparative assessment of different human protein-protein interaction networks. This analysis shows that the current maps have only a small, but nevertheless significant overlap. Furthermore, we detected intrinsic tendencies which are necessary to consider in future application of these maps. We also observed that some previous findings for network structures in lower eukaryotes cannot be reproduced for current human interaction maps and a reevaluation of network concepts might be warranted for the human interaction network.

Protein interactions underlie most of the molecular mechanisms. Intensive research in recent decades has revealed many details of the fascinating multifaceted capacity of proteins to gain divers functionality by interaction. Although these efforts have supplied us with a tremendous amount of information for single proteins, they also indicated that most proteins function in a highly cooperative manner. Thus, comprehensive knowledge of protein interactions is crucial for a deeper understanding of the complex cellular mechanisms and a prerequisite for accurate models in systems biology.

Large-scale maps of protein interactions aim to constitute a scaffold for such comprehensive models. Similarly to fully sequenced genomes serving nowadays as fundament for genetics, complete maps of protein-protein interactions (termed also protein interactomes) could serve as a solid basis for a systematic modeling approach of cellular processes. In contrast to the highly successful mapping genome projects, however, the progress in revealing interactomes has been much slower, especially for the human interactome. Only recently, there have been a growing number of both experimental and computational efforts to gain systematical maps of human protein interactome. A major task will be the integration of these distinct protein networks. However, caution is required as studies of interaction maps in lower eukaryotes revealed a surprising divergence between different maps [1]. Thus, critical comparisons are

necessary regarding the congruency of different data sources.

We present here a first comparative assessment of eight different large scale human protein-protein interaction networks [2-9]. These maps were derived either from Y2H-assays [2,3], literature reviews [4-6] or extrapolated on the basis of homologous interactions in other organisms [7-9]. The analysis showed that the current maps have only a small, but nevertheless significant overlap. Whereas the majority of proteins can be found in multiple maps, this is only the case for less than 10% of the interactions making the maps largely complementary. We detected strong sampling and detection biases linked to the method of generating the maps. For example, RNA binding proteins were overrepresented in orthology-based maps, whereas signal transducers were overproportionally sampled in literature-based maps. A significant depletion of membrane proteins was observed in all networks and not only in Y2H-based maps as expected. Moreover, maps were generally more concurrent if they were based on the same method. These findings will be necessary to consider in future application of these maps.

We also observed that some previous conclusions for network structures in lower eukaryotes cannot be reproduced for humans. For example, the conjecture that the number of interactions is correlated with essentiality of proteins cannot be generally supported for human interaction networks [10]. Equally, protein hubs may not be separated as previously reported indicating that present view of modularity in networks may have to be modified [11]. The results suggest that a re-evaluation of concepts regarding network structure and evolution may be warranted. A more dynamic view of network evolution is also indicated by a comparison which we performed for hubs in different maps. It proposes that hubs can be divided into different evolutionary categories. Ancient hubs include proteins of core machineries as the proteasome and the polymerases whereas evolutionary novel hubs are mainly involved in signal transduction and regulation. This classification indicates that the current theory of simple preferential attachment may be not sufficient, but that network hubs have arisen to meet the particular requirements of an organism [12].

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