

Chapter XV

Dynamics of Protein–Protein Interaction Network in Plasmodium Falciparum

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ABSTRACT

Integration of organism-wide protein interactome data with information on expression of genes, cellular localization of proteins and their functions has proved extremely useful in developing biologically intuitive interaction networks. This chapter highlights the dynamics in protein interaction network across different stages in the lifecycle of Plasmodium falciparum, a malarial parasite, and the implication of the network dynamics in different physiological processes. The main focus of the chapter is the integration of information on experimentally derived interactions of P.falciparum proteins with expression data and analysis of the implications of interactions in different cellular processes. Extensive analysis has been made to quantify the interaction dynamics across various stages, as well as correlating it with the dynamics of the cellular pathways involving the interacting proteins. The authors' analysis demonstrates the power of strategic integration of genome-wide datasets in extracting information on dynamics of biological pathways and processes.

INTRODUCTION

A living cell comprises of several protein assemblies such as DNA polymerases, spliceosomes and scaffolding protein complexes involved in signaling pathways. These machineries can be viewed as multi-protein complexes (Spirin & Mirny, 2003) comprising of interacting proteins as it is illustrated in the example of RNA polymerase

which is responsible for mRNA synthesis. The core complex of RNA polymerase is made up of five subunits namely, two α , β , β' and ω subunits with σ subunit included in one of the functional forms. Together all these subunits interact to give rise to an active RNA polymerase. Presence of each of these subunits allows the polymerase to recognize a specific promoter, initiate transcription, polymerize RNA on a DNA template, continue polymerization till the end of a gene and finally terminate polymerization. Thus evolution of large multi-protein complexes enables a system to carry out multiple processes with greater fidelity in a highly regulated manner. Apart from the existence of such multi-protein assemblies transient protein-protein interactions are also very commonly seen during biological processes. Thus, a cellular event is most often an outcome of several protein molecules interacting in an ordered manner (Alberts, 1998). Given the significance and widespread occurrence of protein-protein interactions in cellular processes it is natural to expect a large proportion of proteome of an organism is involved in mediating protein-protein interactions and carry out different biological processes in an efficient and regulated manner (Legrain, Wojcik & Gauthier, 2001). Apart from using protein-protein interactions to study the complexity of an organism it can also be immensely helpful in identifying suitable drug targets in pathogens based on the importance of the interactions for the survival of the pathogen. Abrogation of critical interactions could lead to successful elimination of the pathogen. In addition to deciphering interactions existing within an organism, protein-protein interactions are also now being identified between pathogens and their hosts (Davis et al., 2007; Krishnadev & Srinivasan, 2008) since the process of invasion of a host cell by pathogen depends on series of protein-protein interactions between the host and the pathogen.

In the recent past several experimental strategies have been developed to study protein-protein interactions (Shoemaker & Panchenko, 2007a). Identification of protein interactions can be performed either at a small scale leading to identification of a few protein-protein complexes or at a large scale identifying interactions at genomic scale. Techniques such as yeast-two-hybrid (Y2H) (Fields & Song, 1989; Golemis, Serebriiskii & Law, 1999) aim towards building the whole organism protein-protein interaction map, synonymously referred as “interactome” (Schwikowski, Uetz, & Field, 2000). Such interactomes have been constructed for many model organisms such as *C.elegans* (Li et al., 2004) and *D.melanogaster* (Giot et al., 2003). Apart from Y2H there are other experimental approaches such as affinity purification and protein chips (Zhu et al., 2001) to obtain high throughput protein interaction data. Although each of these methods has many advantages and shortcomings, Y2H is one of the popular means for obtaining interaction data at genomic level. The Y2H approach is simple whereby ability for two proteins to interact is checked *in vivo* in the yeast system by coupling protein interaction with the expression of a reporter gene. Thus the approach allows for identifying interactions in a manner they would occur in a cell. However Y2H method itself has several limitations. For example, proteins initiating transcription by themselves cannot be targeted in Y2H experiments; and the use of fused sequence products can impose difficulties as fusion can change the structure of a target protein (Shoemaker & Panchenko, 2007a). In addition, protein folding and posttranslational modifications can differ between yeast and other organisms. This makes it difficult to screen proteins from mammalian and prokaryotic cells using Y2H and it is difficult to employ Y2H for cytoplasmic and membrane proteins. Apart from inherent inability to detect all the interactions, not all the interactions reported by Y2H may occur *in vivo*. Such false positive interactions may exist due to indirect interactions between proteins which are spatially proximal but physically not interacting. Thus extensive efforts have been made to reduce false positives and increase the coverage of the interactions detected by Y2H (Bader et al., 2004; Deane et al., 2002; Wojcik, Boneca & Legrain, 2002).

Experimental approaches to identify interactions are difficult and time consuming and hence have not been successfully adopted in obtaining interaction maps for many organisms of interest. Till date no interactome map exists for a large majority of organisms including important pathogens like *M.tuberculosis*. Thus there is a need for computational exploration of protein – protein interactions which in many cases are of reasonable accuracy (Schachter, 2002; Gomez & Rzhetsky, 2002). Interaction maps have been derived computationally for various organisms based on the homology of a pair of proteins in the target organism with an interacting pair of proteins in a template organism (Interologue mapping) (Itzhaki et al., 2006). The approach can work well in the case of two closely related organisms since the physiologies of such organisms are similar and hence the protein-protein interaction patterns would be similar (Mika & Rost, 2006). In the case of distantly related organisms, additional filtering is necessary to assess the biological feasibility of proposed interactions. Many groups have successfully made use of integrated databases for computational detection of protein-protein interactions (Lee et al., 2006;

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