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NEWS AND VIEWS

A global protein–lipid interactome map

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Cellular processes are mediated by complex webs of interactions between macromolecules and metabolites, the complete set of which is often referred to as 'interactome network'. Global and local properties of interactome networks appear to integrate genotypes into biological functions and phenotypes (Gavin *et al*, 2006). So far, empirical mapping efforts of cellular interactome networks have largely focused on interactions between macromolecules, such as protein–protein and DNA–protein interactions. Corresponding efforts to chart interactome networks between macromolecules and metabolites (sugars, nucleotides, amino acids or lipids) are still in their infancies. Lipids represent a large and diverse class of bioactive metabolites with mostly unknown molecular modes of action. Current knowledge about their 'connectivity' represents solitary islands on a vast open ocean rather than a comprehensive interconnected atlas.

In an article just published in *Molecular Systems Biology* (Gallego *et al*, 2010), Gavin and colleagues describe a systematic screening strategy for protein–lipid interactions in *Saccharomyces cerevisiae*. Over 500 protein–lipid associations were catalogued, shedding light on the elusive modes of action of several bioactive lipids, and uncovering a novel dual-binding specificity of a PH domain based on a novel structure. Additionally, a complete linkage analysis of protein–lipid-binding fingerprints was modeled as predictors of protein localization (Figure 1).

The diversity of lipid-binding protein domains (LBDs) and the considerable list of human diseases attributed to alterations in protein–lipid interactions (Charbonnier *et al*, 2008) both underline the value of this new data set. Going beyond earlier studies that used either smaller sets of lipids or isolated LBDs, this study employed an unbiased and systematic large-scale biochemical screen. To identify lipid-binding fingerprints, the authors utilized a comprehensive set of soluble proteins expressed as carboxy-terminal tandem-affinity-purification-tag fusions in *S. cerevisiae* (Gavin *et al*, 2006) and probed these tagged proteins on miniaturized nitrocellulose arrays displaying a comprehensive set of lipids and metabolic intermediates, representing the main lipid classes and metabolic pathways in yeast. Query proteins were LBD-containing proteins, lipid-regulated enzymes and several arbitrarily chosen soluble proteins. Gallego *et al* estimated the accuracy of their screen by taking advantage of the fact that genetic interaction networks partially correlate with physical interaction networks. Reassuringly, they observed that the protein–lipid interactions overlap significantly with known genetic interactions between lipid metabolizing enzymes and the target proteins analyzed. Furthermore, ~70% of the interactions were novel or unexpected. Using sequence searches for remote homologues of known LBDs, the authors identified cryptic LBDs in proteins not previously known to contain LBDs and confirmed these using a more physiological liposomal membrane recruitment assay. A group of proteins that interacted with sphingolipids shed light on the elusive mechanism of action of these bioactive lipids. Live-cell imaging and a functional myriocin inhibition assay of sphingolipid metabolism uncovered new sphingolipid targets that were successfully validated *in vivo*, including PH domain containing proteins such as Slm1. A newly presented Slm1 PH domain crystal structure revealed a new lipid recognition mechanism that may function as a 'coincidence sensor', integrating metabolic signaling pathways via cooperative binding of phosphatidylinositol phosphates and phosphorylated sphingolipids. The reported protein–lipid-binding fingerprints may ultimately serve as predictors of interactions and dynamic processes at biological membranes and may help to understand membrane assembly, structure and function (Figure 1).

As with any far-reaching investigation, more new questions are uncovered than old questions answered. The growing knowledge of the 'transcriptome' enables correlation studies with protein–protein interaction networks. Yet, how are lipid metabolism and protein–lipid interactions dynamically regulated? Post-translational protein modifications (PTMs) are crucial signaling modifiers, and proteomics approaches have proven powerful in mapping comprehensive PTM signatures. To what extent can PTMs impinge on lipid-binding fingerprints? How may protein–lipid-binding profiles influence hypotheses previously derived from protein–protein interaction networks? An important insight from whole proteome interactome studies was the revelation of the modularity of the proteome, wherein multifunctional proteins or protein

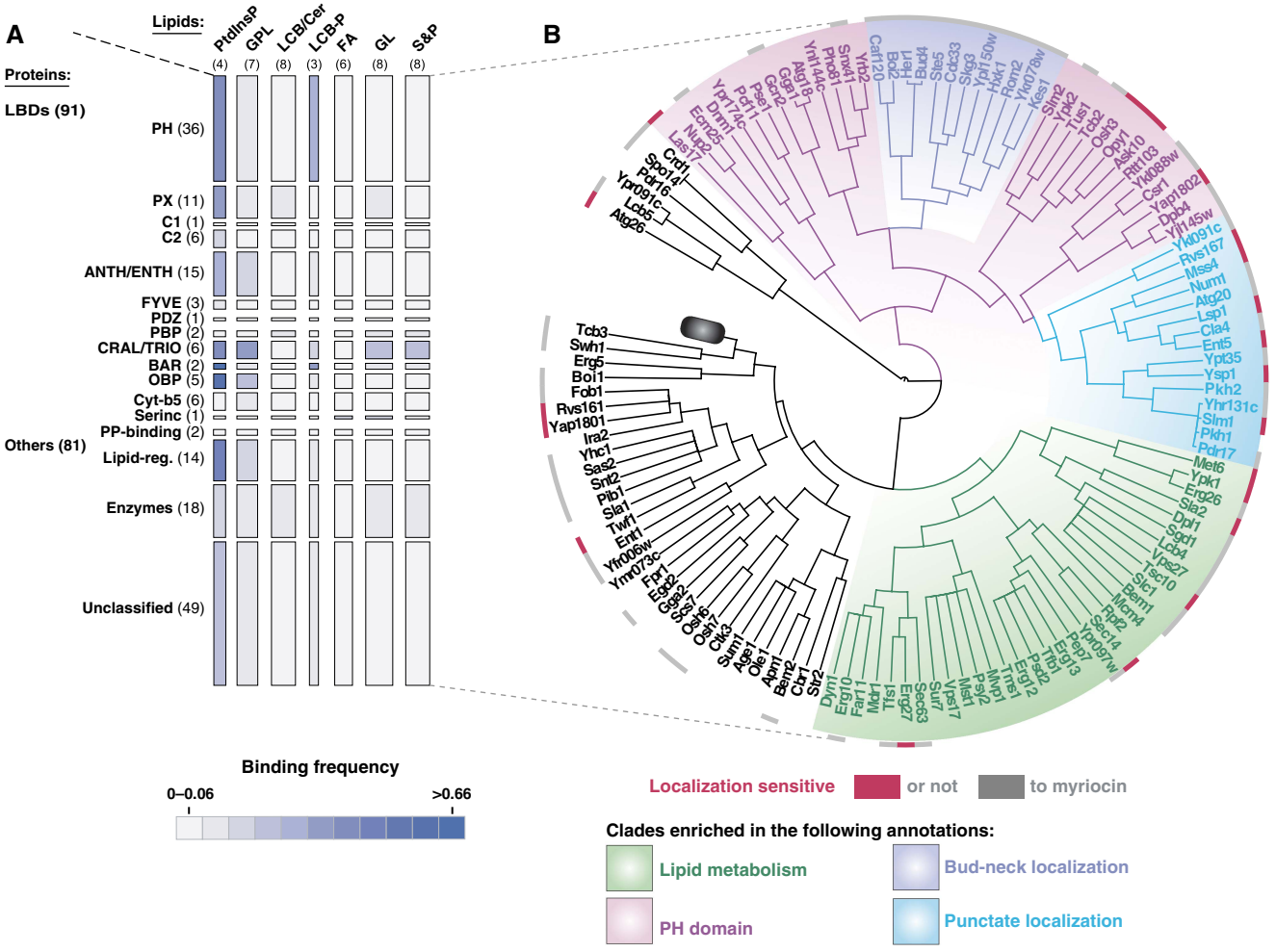

Figure 1 Yeast protein–lipid-binding fingerprints as predictors of protein localization, domains and functions. (**A**) Yeast protein–lipid-binding map summarizing protein–lipid-binding frequencies, where lipids and proteins are grouped according to their metabolic pathways and LBDs, respectively. Box sizes are proportional to the number of proteins and lipids per group and the scale represents normalized number of interactions. (**B**) Complete linkage clustering of lipid-binding fingerprints reveals clades enriched in the annotations lipid metabolism (green), PH domain (pink), Bud-neck localization (violet) and punctate localization (turquoise). Adapted from Gallego *et al* (2010).

subcomplexes (modules) form components of various molecular machines such that a protein with a given annotated function might adopt a completely new function under different circumstances, a phenomenon called protein 'moonlighting' (Gavin *et al*, 2006). The coincidence sensor role of the PH domain identified adds comparable complexity to lipid signaling. While a single protein or domain may potentially interact with different lipid classes, 'lipid moonlighting' might add further complexity to lipid biology and protein–lipid profiles.

The emerging extent of protein–lipid interactions suggests an intricate interplay between proteins and lipids. Scientists are just starting to learn how protein networks are altered in disease and how they can be readjusted with therapeutic agents (Balch *et al*, 2008). Protein–lipid interactions represent a largely unexplored and undefined therapeutic target space. What roles do lipids play, what are their protein-binding profiles and how are these altered in diseases? Only the integration of complementary transcriptome, proteome and metabolome data sets will leverage the understanding of the higher-level organization of the interactome. Three research groups recently put together a systems biology 'tour de force' (Glass *et al*, 2009) towards a complete characterization of the minimal bacterium *Mycoplasma pneumoniae* (Güell *et al*, 2009; Kühner *et al*, 2009; Yus *et al*, 2009). Gallego *et al* now provide the important metabolome data set that complements existing large-scale macromolecular 'interactomes' of the eukaryotic model *S. cerevisiae* (Gavin *et al*, 2006; Yu *et al*, 2008). Longer term, 'deep dipping' into metabolite interaction networks, when combined with gene expression, proteomic, genetic and physical interaction data as well as functional and quantitative parameters, will place lipid biology as an integral component of the global molecular wiring of the cell (Costanzo *et al*, 2010). A holistic molecular interaction map of the cell as an ultimate translation of the blueprints of life will eventually help to navigate, understand and tackle biological processes and their perturbations in human disease.

Conflict of interest

The authors declare conflicting interests. In addition to their affiliation with the Center for Cancer Systems Biology (CCSB) and Department of Cancer Biology, Dana-Farber Cancer Institute and the Department of Genetics, Harvard Medical School (Boston, MA), Marc Brehme is an employee and Marc Vidal is a Scientific Advisory Board member of Proteostasis Therapeutics, Inc. (Cambridge, MA).

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