SYSTEMS BIOLOGY

The power of 'weak' interactions

A map of mammalian protein interactions highlights the importance of substoichiometric interactions.

Driven by the understanding that proteins do not function in isolation, researchers have made many efforts to map protein-protein interactions in biological systems. Work from the groups of Matthias Mann and Anthony Hyman, at Max Planck Institutes in Martinsried and Dresden, respectively, has now yielded a quantitative map of the interaction partners of about 1,100 proteins in human cells. About half of these baits were mouse proteins. Notably, all baits were expressed at close to endogenous levels from BAC transgenes in stable HeLa cell lines. Avoidance of overexpression is critical for quantitative interaction studies, because protein complexes are perturbed as a consequence of a drastic increase in the abundance of one of the interaction partners. The baits were also tagged with GFP, permitting standardized immunoprecipitation followed by mass spectrometry and the use of sophisticated label-free quantitative methods to identify interacting proteins.

After statistical analysis to define significance thresholds, the researchers reported a network of 28,504 interactions among 5,462 proteins. They then used their quantitative data to probe the abundance of proteins in the network and the stoichiometry of complexes. They introduce the stoichiometry plot, in which the abundance and interaction stoichiometries of all interactors for a given bait protein are plotted against each other. This gives a quick visual summary of many types of complexes, including 1:1 complexes where bait and prey have similar abundance (which are likely to be stable) as well as complexes where the prey is substoichiometric to the bait. Perhaps not surprisingly, the researchers observed many more interactions in the latter category. This is probably an underestimation, as affinity-based interaction networks are unlikely to capture the weakest interactions.

The researchers used independent methods to show that substoichiometric complexes reflect biophysically weak, or transient, interactions. What is more, they show that these interactions counterintuitively function as the 'glue' that holds networks together. Simulated removal of substoichiometric protein interactions more rapidly resulted in the network falling apart, in comparison to removal of strong or random interactions. Although the links that hold substoichiometric complexes together may be fragile in one sense, they seem to be key for integrating different functions in the cell.

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RESEARCH PAPERS

Hein, M.Y. *et al.* A human interactome in three quantitative dimensions organized by stoichiometries and abundances. *Cell* **163**, 712–723 (2015).

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