

SYSTEMS BIOLOGY

An expanded human interactome

An expanded catalog of binary biophysical interactions between human proteins.

Most biological processes involve molecular interactions. Although there have been many studies of one such interaction type, protein-protein interactions, the current list of binary human protein interactions is thought to be far from the 'complete' interactome.

Frederick Roth at the University of Toronto and Marc Vidal at the Dana-Farber Cancer Institute, and colleagues, now describe an expanded data set of binary biophysical interactions between human proteins. Building on extensive experience using the yeast two-hybrid (Y2H) method to make high-quality interactome maps, the team probed all binary interactions between proteins encoded by about 13,000 genes. Benchmarking assay performance with literature-curated reference sets, they observed no loss of precision or sensitivity at this scale. After validation

of the interactions with orthogonal assays, Roth, Vidal and colleagues report a map of almost 14,000 high-quality interactions between 4,303 proteins.

When they compared the resulting data set to the set of about 11,000 high-quality binary interactions in the literature as of 2013 ('high quality' is here defined as being supported by multiple lines of evidence), the authors saw a marked difference in the distribution across the 'publication-ranked interactome space'. Proteins on which many papers have been published have many literature-reported interactions, whereas proteins on which few papers have been published have an apparently sparse interactome. The new Y2H data set, by contrast, is more homogeneous, reporting interactions across this spectrum.

This suggests that the 'sparse zones' in literature-curated interaction data at least partly reflect sociological biases rather than biological laws: heavily studied proteins are

more studied also in terms of their interactions. (It should be noted, that the Y2H data set also has biases; for instance, it is depleted of membrane proteins.) The quality of the Y2H interactions in sparse zones is no lower than that in dense zones.

What of the biological relevance of the interactions? The Y2H assay reports possible physical interactions between the assayed proteins within the heterologous confines of the yeast nucleus. The expanded data set, Roth and colleagues show, is enriched for protein pairs with features indicating that their interactions are likely to be meaningful. But further analysis is always necessary to determine whether a particular interaction occurs biologically and if it is important for the cell types or process under study.

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RESEARCH PAPERS

Rolland, T. *et al.* A proteome-scale map of the human interactome network. *Cell* **159**, 1212–1226 (2014).