

SYSTEMS BIOLOGY

Ancient protein complexes revealed

A systematic analysis of protein-complex composition across a billion years of evolution reveals a spectrum of conservation.

Comparative analyses of protein-protein interaction networks from *Escherichia coli* to humans have shown that such networks are conserved and relatively slow-evolving. Yet open questions remain about whether physical interactions are preserved between evolutionarily distinct species, what these protein complexes are and what they do.

These are some of the questions that Andrew Emili of the University of Toronto, Edward Marcotte of the University of Texas at Austin and their colleagues set out to answer. In a previous study, the team developed a standardized approach to determine protein membership in soluble human complexes, using biochemical fractionation followed by mass spectrometry. In their new work, seeking to discover which of the human protein complexes had been conserved throughout

history, they applied the approach to eight species—mouse, frog, fly, worm, sea urchin, sea anemone, amoeba and yeast—spanning a billion years of evolution.

With this massive set of experiments, the researchers identified and quantified 13,386 protein orthologues. They developed a machine learning–classification method to pull out interactions that were conserved between human proteins and their worm, fly, mouse and sea urchin orthologues (the data from the other four species were used to benchmark the approach). Their final network contained 16,655 human co-complex interactions with supporting evidence from at least two other species.

Next, the team used these results to predict co-complex interactions between orthologous protein pairs for an additional 122 eukaryotes, some of which they validated using affinity purification coupled with mass spectrometry. Clustering analysis led to

some interesting conclusions. For example, despite the fact that the majority of human proteins arose in animals, they found that by and large, most stable human protein complexes were likely inherited from a unicellular ancestor. Membership in such ancient complexes was either conserved or mixed with animal-specific components, and these complexes tended to be abundant, ubiquitously expressed and functionally associated with core cellular processes. The relatively rare complexes consisting solely of proteins that arose in animals, in contrast, tended to have functions strongly linked to multicellularity.

The team's draft protein-complex conservation map is available at <http://metazoa.med.utoronto.ca> and should suggest interesting avenues for future analysis.

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RESEARCH PAPERS

Wan, C. *et al.* Panorama of ancient metazoan macromolecular complexes. *Nature* **525**, 339–344 (2015).