

## Highlight: The Chaperone Network—Evolution’s Helping Hand

Danielle Venton

Corresponding author: E-mail: danielle.venton@gmail.com.

**Accepted:** 28 March 2012

Few courting couples today mourn the demise of the social chaperone. Yet, these party guards played, in their way, a useful role: escorting young people into society and barring “unwanted interactions.” The work of guides and separators is so important, in fact, that a kind of biomachinery crucial for life shares its name and partial job description with the venerable chaperones of old.

Chaperone proteins have, for decades, been known to give newly translated proteins a helping hand, aiding in their folding and integration in the cell. New work suggests that chaperone proteins may deserve more credit yet. Chaperone proteins, as studied in the yeast *Saccharomyces cerevisiae*, appear to be organized into networks that mediate how quickly different classes of proteins evolve.

“Our key new finding,” says Tal Dagan, research group leader and senior author of a study published in *Genome Biology and Evolution* (Bogumil et al. 2012), “is that the chaperone interactions divide yeast proteins into groups, these are different by expression level and evolutionary rates.”

Dagan and her team, based out of the Institute of Molecular Evolution at Heinrich-Heine-Universität Düsseldorf, also suggest that chaperones have a cumulative impact on the evolutionary rate. That highly expressed proteins have quick translation and slow evolution is well established. Dagan’s team is the first to propose a mechanism for why less-expressed proteins would be translated slower and have higher evolution rates: they are more dependent on chaperones to take care of them. Highly expressed proteins, on the other hand, are self-folding and less tolerant of mutations that would alter their structure.

“Tell me who helps you to fold and I will tell you how fast you can evolve,” she says. “We found a biological mechanism that ties these correlations together and creates variation over time in genomes.”

This latest study follows on years of related work from this and other teams. In the early 1990s, Susan Lindquist helped show that in vitro chaperone proteins can buffer against quick physiological changes (part of the reason they are

often called “heat shock proteins”) and can confer higher fitness for the organism. Chaperones allow their substrate proteins to accumulate more mutations, shaping and working the translated amino acid chain into its functional conformation. If a new mutation has made the protein a bit unstable, the chaperone’s “helping hand” may be able to help it retain its shape.

“If it happens in vitro, we thought it should happen in vivo too,” Dagan says. In an earlier study, they found such interactions in prokaryotes and “we decided to go one step further and look for it in eukaryotes, the next evolutionary phase.”

Her team was fortunate, Dagan says, because in 2009, Yunchen Gong and colleagues published a remarkable dataset: an atlas of chaperone–protein interactions in *S. cerevisiae*. They looked for correlations among the 21,687 interactions documented between chaperones and their substrates, primarily proteins. For several months, the team looked for patterns using standard statistics, but nothing much showed up.

Each chaperone, explains David Bogumil, a coauthor and PhD student at the Institute, can have between one and more than 2,500 interaction partners. A protein can interact with up to 25 separate chaperones. Realizing that this information represented a web of relationships, they transformed the data into a network. And there, within the larger network, they found ten distinct, smaller groups. These smaller groups represented one or more chaperones and the proteins they most commonly interacted with.

“It’s a sensible system,” Bogumil says. “Chaperones have to split up the work to make it efficient.”

These ten communities differed in their physiochemical properties, having distinct proportions of amino acids and secondary structure properties. For example, the proportion of alpha-helical structures is significantly different among the communities.

“Why should we have these differences?” asks Dagan. “It makes a lot of sense. Chaperones supply a service, they act as a hub.” Because many proteins interact with the same

chaperone, they need something in common, some clue, to hold the interaction together.

“Nobody knows yet what the chaperone sees [or recognizes] in the intermediate structure of the protein,” Dagan says, speculating that something in the protein’s secondary structure or amino acid composition allows it to be recognized. It is perhaps this need for its chaperone, this waiting around for help to come, that explains why chaperone-folded proteins are generally translated more slowly. In the absence of chaperone help, these proteins could aggregate, a toxic situation for the cell. (Several neurodegenerative diseases, Parkinson’s, Alzheimer’s, and Huntington’s, e.g., are due to protein aggregations in neurons.)

“What we think we’re seeing here, why we think this evolved,” Dagan says, “is that there is a need to synchronize protein translation with folding.”

Mario Fares, a researcher at University of Dublin, Trinity College, not connected with this study, believes chaperones are key in protein evolution but is unconvinced that Dagan and her colleagues have uncovered the causal mechanism for evolutionary rates. The observed correlations between expression, evolutionary rates, and codon biases are not,

Fares says, mutually exclusive and not evidence of cause and effect.

“I do believe the chaperones are real sentinels of the cell and have a large role in controlling evolution,” Fares says. “And along with the authors, I think our understanding of chaperone’s role in evolution is in its infancy.”

Both Fares and Dagan believe a thorough understanding of protein–chaperone interactions will have major implications for synthetic biology. With a fuller knowledge of their interactions, useful chaperones might be engineered, allowing more control over protein and cell function. Capitalizing on chaperone’s ability to buffer the effects of heat shock, for example, plants could be made more resistant to dehydration stress.

“We still have plenty of interesting questions to look at,” Bogumil says. “We’re already started on the next study.”

## Literature Cited

Bogumil D, Landan G, Ilhan J, Dagan T. Chaperones divide yeast proteins into classes of expression level and evolutionary rate. *Genome Biol Evol.* Advance Access published March 14, 2012, doi:10.1093/gbe/evs025