Probe human diseases in yeast? Possibly, protein study suggests

May 10 2011

(PhysOrg.com) -- The molecular-level workings of proteins are surprisingly similar across a wide range of organisms, from humans to fungi and plants, research by University of Michigan evolutionary biologist Jianzhi "George" Zhang and colleagues suggests.

This finding raises the possibility of using much simpler organisms, such as yeast, to study the mechanisms underlying human disease.

The study is scheduled to be published online in the Proceedings of the National Academy of Sciences during the week of May 9.

Proteins—large, complex molecules that play crucial roles in the structure, function and regulation of the body's tissues and organs—are made up of hundreds to thousands of building blocks called amino acids, which can be combined in a multitude of different sequences. Much research has focused on comparing sequences of a particular protein—say, the oxygen-carrying protein hemoglobin—in different species and then, based on what's known about the evolutionary relationships of those species, figuring out how much or little the protein has changed over time.

But such studies reveal only changes in protein sequence. What about changes in protein function? Those are more difficult to measure and compare, says Zhang, because of the wide variety of roles proteins perform. However, he and his coauthors came up with the idea of using interactions between pairs of proteins, known as protein-protein

interactions or PPI, as an index of protein function that could be used to make comparisons among species and measure the rate of protein function evolution.

"Many proteins function through interactions with other proteins, and in the last decade people have systematically surveyed PPI in a number of model organisms," said Zhang, a professor of ecology and evolutionary biology who is also affiliated with the Center for Statistical Genetics in the School of Public Health and the Center for Computational Medicine and Bioinformatics at U-M Medical School. His first thought was to use data from those surveys, but the methods used to collect the data made them less than perfect for his purposes.

"The surveys have used high-throughput methods, which are fast but suffer from high false-positive and false-negative errors," Zhang said. "False positive means that the interaction actually does not exist, but somehow you saw it in your experiment; false negative means an interaction actually does exist, but you didn't detect it in your experiment.

"So we thought perhaps we should do an experiment in which we use a low-throughput method, which is more accurate."

They started with Saccharomyces cerevisiae, a type of budding yeast used since ancient times in baking and brewing, whose protein-protein interactions have been well studied. The idea was to find a pair of proteins in S. cerevisiae that are known to interact with each other, then look at another species of yeast that possesses the same proteins and see if they also interact in that species. The other species the researchers chose was a related yeast, Kluyveromyces waltii. Already knowing that S. cerevisiae and K. waltii diverged about 150 million years ago, Zhang's group could use the protein interaction data in the two species to estimate the rate of protein function evolution.

"If we check a lot of interactions and see whether they've changed or stayed the same in the two species, we get an idea of what fraction of interactions are 'conserved' over the course of 150 million years," Zhang said. For the 43 pairs of proteins they were able to compare, Zhang's group found no differences in interactions between the two species of yeast. "So they were all conserved; the evolution rate is zero."

Next, the researchers wanted to know whether protein function evolved as slowly in other species. They took data from two studies by other researchers—one using high-throughput techniques, the other using a low-throughput method—and reanalyzed them in a way that controlled for false positives, false negatives and other confounding issues. Combining all the data, which encompassed yeasts, the roundworm Caenorhabditis elegans and mammals (mouse and human), they determined that the evolutionary rate of protein molecular function was strikingly slow.

"Compared to sequence evolution, there's about a one thousand-fold difference," Zhang said. "That means that on average, it requires about one thousand amino acid changes in a protein to have one change in a protein-protein interaction."

That makes biological sense, Zhang said. "We know that the most basic cellular processes are similar among a wide array of species, from single-cell organisms to multi-cellular, very complex species, and since protein-protein interactions are involved in almost all of these processes, it is not unexpected that PPI is also highly conserved. It is likely that the extreme conservation of PPI is one of the bedrocks of the conservative nature of life."

Zhang stressed that while the molecular functions of proteins are quite similar from species to species, the physiological roles of proteins and their effects on organisms can vary widely. For example, in humans,

certain proteins have been implicated in an inherited condition called Waardenburg syndrome, which is characterized by deafness and pale skin, hair and eyes. In Arabidopsis, a plant in the mustard family, those same proteins are present despite the lack of ears, skin, hair, and eyes, but they're involved in the plant's response to gravity.

"The corresponding proteins participate in very different physiological processes, yet, if the molecular functions of the proteins are conserved, you could still use plants or yeast to understand the molecular mechanisms involved in human disease, to see what molecular cellular processes are affected when these proteins malfunction," Zhang said.

More information: www.pnas.org/

Provided by University of Michigan