Examination Of Internal 'Wiring' Of Yeast, Worm, And Fly Reveals Conserved Circuits

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Researchers in California, Israel, and Germany have compared three distantly related species - baker's yeast, a worm, and the fruit fly - and reported that protein "wiring" connections in one species are often conserved in all three. This first-of-its-kind analysis of three higher level organisms published in the February 8 issue of *Proceedings of the National Academy of Sciences* supports both the concept of a basic wiring diagram for all eukaryotic cells, and the idea that more selective pharmaceuticals could be designed to tweak the wiring plan of human cells to more effectively treat diseases while also generating fewer side-effects.

"We're basically now able to open the hood of yeast, worm, and fly cells and look at the protein interactions inside," said Trey Ideker, a bioengineering professor at the University of California, San Diego and one of the nine co-authors of the paper. "Ultimately, this type of wiring analysis will help us more fully explain how the diversity of life developed on the planet, and more practically, how a pathogen differs from its human host, or a diseased cell differs from it healthy counterpart at the most informative level of detail."

For centuries, systematic comparisons of animal, plant, and microbial species was based on painstaking measurements of anatomic features. Beginning in the late-1970s, DNA sequencing technology permitted biologists to identify the precise subunit sequence of every gene in the genomes of everything from malaria pathogens and mosquitoes to mouse and human. Databases of genomic information have been combined with databases that list the precise subunit sequence of proteins as well. Cross-species DNA and protein comparisons have become routine for all biologists with computerized search programs, the most popular of which is called BLAST.

The wiring analysis reported in *PNAS* was made possible with yet another type of database called the Database of Interacting Proteins. That repository contains the results of tens of thousands of laboratory measurements of physical interactions of proteins in more than 100 species. Ideker and his colleagues developed a computerized tool called PathBLAST to search through the Database of Interacting Proteins for protein interactions that are conserved in the three most thoroughly studied species: yeast, worm, and fly,.

The research team completed a rigorous statistical comparative analysis of a total of 14,145 yeast (*Saccharomyces cerevisiae*), worm (*Caenorhabditis elegans*), and fly (*Drosophila melanogaster*) proteins with 38,965 known interactions. Their PathBLAST tool generated a list of similar proteins in the three species that were involved in similar interactions: there were 183 protein clusters and 240 communication pathways conserved in all three. The finding suggests that only 0.5 percent of the protein clusters and communication pathways are conserved in the three species, but Ideker estimated that as many as 80 percent of the actual protein interactions have yet to be discovered.

"We are currently limited by the information and technology we have to date, so when we open up the hood of these three organisms we actually have selective and poor vision," said Ideker. "Nevertheless, when we found protein interactions and communication pathways conserved across all three species we were more confident that we are seeing something real."

Biologists have known for many years that in even distantly related species, nature doesn't reinvent the wheel. Similar proteins involved in essential cellular functions are often similar across species. "This new result indicates that the way in which the most functionally important proteins are *assembled* into machinery from one species to another is also, to a certain degree, conserved," said Ideker. "The circuitry is not exactly the same. In fact, there are striking differences that warrant more investigation."

The team included Roded Sharan, a computer scientist currently at the Tel-Aviv University in Israel; Tanja Kuhn and Peter Uetz, researchers at the Institute of Genetics in Karlsruhe, Germany; Ideker, Silpa Suthram, Ryan M. Kelley, Scott McCuine, and Taylor Sittler at UCSD; and Richard M. Karp, a computer scientist at the University of California, Berkeley.

Their analysis revealed conservation and overlap in yeast, worm, and fly in 71 distinct "network regions" that included such essential functions as protein degradation, RNA polyadenylation and splicing, protein phosphorylation and signal transduction, DNA synthesis, nuclear-cytoplasmic transport, and protein folding. Such networks enriched for several functions suggested to the researchers that cellular processes may work together in a coordinated fashion.

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-Trey Ideker, UCSD bioengineering professor

In contrast, the team did not find in yeast a network they found in both worm and fly that is involved in the guidance of nerve cell axons to their synaptic targets, or junctions, with other nerve cells. The process, considered an initial step in the development of the central nervous system, would not be needed by lower organisms, such as yeast, which don't have nerves.

Ideker predicted that protein-interaction studies will soon become indispensable tools for biologists seeking a better understanding of all cellular functions. He said that just as a species evolved new proteins to give it a selective advantage, it also could have evolved a new combination of existing proteins. Such novel arrangements would have generated new capabilities or changed existing ones.

Pharmaceutical companies have also not had the luxury of protein-interaction databases. They have routinely identified promising new drugs based on trial-and-error screenings of those molecules' ability to completely disable target proteins. Ideker said protein interaction information could help modify that approach to drug discovery. "Maybe the target protein has a good and necessary role in 10 interactions, but the 11th is the only one we would need to eliminate," said Ideker. "What we really want are drugs that interfere with just that one disease-causing interaction."

Systems biologists such as Ideker say their ultimate goal is a comprehensive computer model of how cells work. A description of all protein-interaction circuits would make such a model possible. "We'd like to simulate diseased cell types, such as cancer cells, and then simulate the effects of drugs on those diseased cells," said Ideker. "Ultimately, we think this kind of a systems biology approach will have a very beneficial impact on drug design and human health."

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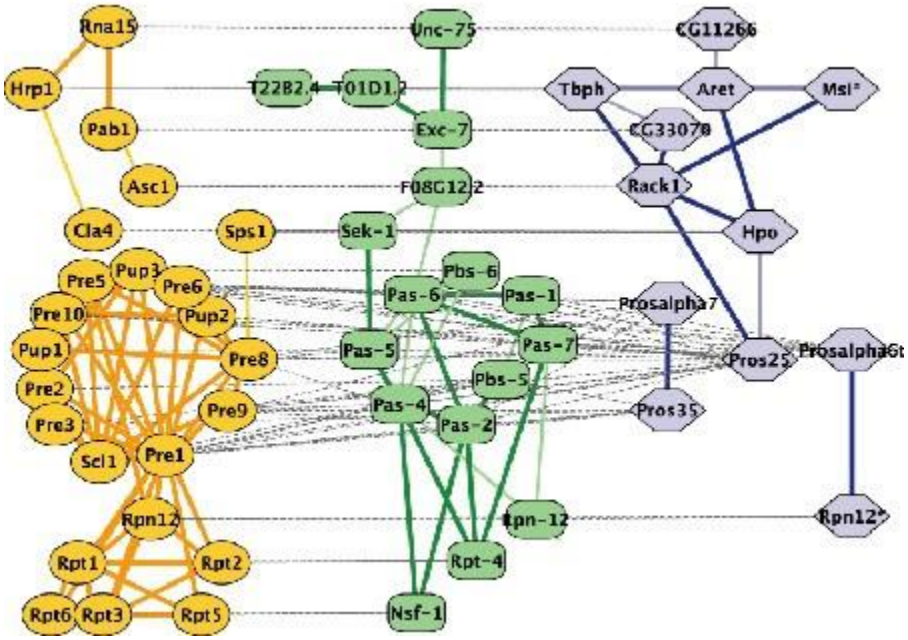
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