STUDY BREAK

Human-Yeast Hybrids: New Visions to Genetic Disorders and Drug Discovery

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Yeast has been a very helpful organism for centuries, especially with respect to fermentation of sugars and production of bread. However, for an even longer time, yeast has been a distant relative of humans having diverged from a common ancestor, about one billion years ago. More than one third of the yeast genes have human counterparts, despite this evolutionary distance. Yeast and human orthologs perform the same or similar functions. Investigations have demonstrated that 9-92% of the amino acid sequences in similar human and yeast proteins overlap. However, even if two genes perform similar functions in two different organisms, it may not be possible to replace some of yeast genes with their human counterpart.

Recently, researchers at the University of Texas have decided to replace a large number of yeast genes with their human orthologs to find out the extent and principles under which human genes can stand in for their yeast counterparts. They have focused on a set of essential genes of the yeast, such as those responsible for metabolism or waste removal. They chose 414 genes of fungal version to replace with the human equivalent and monitored yeast survival. In this way, hundreds of new strains of yeast were created, each with a single human gene. Nearly, half of those engineered strains, so called human-yeast hybrids, were able to survive and reproduce. Edward Marcotte, a professor at the Department of Molecular Biosciences, University of Texas at Austin, stated in a press release that "Cells use a common set of parts and those parts, even after a billion years of independent evolution, are swappable…. It's a beautiful demonstration of the common heritage of all living things."

This type of study has been previously done, but this is the first large-scale study to swap hundreds of ortholog genes. The large number of experiments in this study, allows the researchers to investigate factors determining which genes were most likely to successfully swap with its human counterpart. One hundred and four quantifiable features of the genes, including nucleotide sequences and properties such as protein interactions, mRNA and protein abundances, and transcription and translation rates were studied. It was found that the sequence similarity was not a suitable indicator of replaceability. Instead, they observed that there is a strong association between replaceability and gene modules (groups of genes which work as a unit to accomplish a function), such that if one gene from a specific module is swappable, the other members of its module may as well. This replaceability was verified for 19 components of the sterol biosynthesis pathway. However, it was found that some large protein complexes such as TriC chaperone complex or the DNA replication initiation origin recognition complex were absolutely non-replaceable.

The above findings indicate that if such swapping can take place and a group of module-specific pattern can be replaced, humanizing an entire cellular process in the yeast is very likely. This information could be useful in studying genetic diseases and discovering how mutations can impact a person's health. For instance, the multiple versions of a human gene mutation, responsible for genetic disorders, can be accurately inserted into the yeast and then expose it to various drugs to find the best therapies. Furthermore, this can be simultaneously done for multiple genes. Overall, these so called human-yeast hybrids create an enriched source for the purposes of drug discovery against human genetic disorders. Furthermore, they provide the capacity to perform a multitude of studies investigating the functions of human genes.

More details in:

Systematic humanization of yeast genes reveals conserved functions and genetic modularity. Kachroo AH et al. Science; 2015, 348(6237): 921-925.

Systemic exploration of essential yeast gene function with temperature- sensitive mutants. Li Z et al. Nat Biotechnol; 2011, 29(4): 361-367.

Orthology and functional conservation in eukaryotes. Dolinski K et al. Annu Rev Genet; 2007, 41: 465-507.

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