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Think big, think yeast

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Yeast was the first eukaryote to have its genome sequenced. Technologies that allow the global analysis of cellular function have been pioneered with it, and genome-wide analysis of mRNA and protein abundance, gene function, and protein-protein interactions have been undertaken on it. However, we are still far from a comprehensive knowledge of how yeast functions. Two papers from the Howard Hughes Medical Institute, University of California, San Francisco, in the October 16 Nature report global studies of the yeast proteome that attempt to reveal the location and level of every yeast protein.

Both groups tagged all the annotated open-reading frames (ORFs) in the yeast genome with either green fluorescent protein (GFP) or a tandem affinity purification tag (TAP), followed by their homologous recombination into the yeast genome to each gene's original chromosomal location, thereby creating a collection of protein-tagged strains.

In the first paper, Won-Ki Huh, James Falvo and colleagues systematically tagged the 6234 annotated yeast ORFs with GFP and identified 4156 (75%) that showed GFP signals above background levels. Using florescence micrographs - and in some cases, colocalization with red fluorescence protein (RFP) fusion proteins whose localization was known - enabled the location of every tagged protein within the cell to be determined. These localizations were in 80% agreement with known localizations in the Saccharomyces Genomic Database, gave localization data for 70% of the previously unlocalized yeast proteins (30% of the total proteome), and also identified new localizations for 40% of the tagged proteins. In addition, the authors also observed that genes that tend to be expressed together were found in the same cellular location (*Nature* 2003, **425:**686-691).

In the second paper, Sina Ghaemmaghami and colleagues used a TAP tag, which allowed the expression levels of every tagged protein to be determined with a single antibody. Observable TAP-tagged products were identified for 4251 proteins by Western blot - an approximate 90% overlap with the GFP proteins detected by Huh *et al*. - and verified the expression of 1018 previously hypothetical genes. They also identified about 500 ORFs that were not expressed and had codon compositions different from expressed genes, suggesting they are not real genes. Ghaemmaghami *et al*. further exploited the use of a single antibody for detection to determine the absolute abundance of each protein, which ranged from 50 to more than 10^6 molecules per cell. Finally, when the results were compared with other studies of mRNA expression, the authors observed a consistent average protein to mRNA ratio of about 4800:1 (*Nature* 2003, **425:**737-741).

"All and all, yeast biologists have led the charge in developing approaches to understanding eukaryotic genomes. Huh *et al*. and Ghaemmaghami et al. continue that tradition," comment James A. Wohlschlegel and John R. Yates from the Scripps Research Institute in an accompanying article They further point out that not only has this research provided interesting results, it has also provided the tools for the next round of experiments to understand how an organism functions.

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