

OCTOBER 27, 1998

Yeast Genome Analysis Hints at Complexity of Germ Cell Development

The process by which yeast form spores involves many more genes and is more complex than researchers had expected, according to studies by scientists at the University of California, San Francisco (UCSF) and the Howard Hughes Medical Institute (HHMI) at Stanford University.

Similarities between some of the newly identified yeast genes and mammalian genes indicate that yeast may be a valuable model for learning how germ cells sperm and eggs are produced in vertebrates.

The results of the study, conducted jointly in the laboratories of HHMI investigator Patrick O. Brown at the Stanford University School of Medicine and Ira Herskowitz at UCSF, are published in the October 23, 1998, issue of the journal *Science*.

Previous studies by many different researchers identified about 50 genes that are induced during sporulation—the yeast equivalent of sperm and egg production. The results of expression studies on those 50 genes led researchers to conclude that yeast development occurs in four distinct stages.

Brown's team, however, was the first to attempt a genome-wide study of yeast gene activation during sporulation. Using DNA microarrays containing an estimated 97% of the genes in the brewer's yeast *Saccharomyces cerevisiae*, the group found roughly 500 sporulation-specific genes 10 times more than had been known previously. In addition, the investigators distinguished at least seven temporal patterns of gene transcription, reflecting the sequential progression of spore formation and meiosis.

The researchers induced sporulation by placing *S. cerevisiae* cells in a nitrogen-deficient medium. At seven timed intervals, they measured changes in the concentrations of mRNA transcripts from each of the yeast genes. At the same time, they monitored physical changes in the yeast cells using electron and light microscopy. As a result, Brown's team was able to relate gene expression patterns to the sequence of events involved in sporulation.

The HHMI investigators found that mRNA levels changed significantly during sporulation for more than 1,000 of the yeast's 6,200 genes. About half

of the genes were switched on and half off during sporulation. Furthermore, the timing of gene expression fell into seven temporal stages: rapid/transient, early I, early II, early-middle, middle, mid-late, and late.

Each temporal stage has its own biological correlates. For example, some of the 62 "early I" genes are involved in the replication and recombination of chromosomes, the initial steps in meiosis. Many of the 158 "middle" genes are involved in the mechanics of meiosis: the sorting of chromosomes into four daughter cells in the two special meiotic cell divisions or in the initial stages of spore production. Of the five genes induced in the "late" stage, at least one is necessary to produce the finished spore wall.

Having catalogued the genes involved in sporulation, Brown's team then broadly characterized the roles played by those genes. Knowing that genes with related roles have similar expression patterns, the researchers reasoned that it should be possible to suggest roles for genes of unknown function by studying their temporal relationship to genes of known function: the "guilt by association" approach.

"This study is a door opener," says Herskowitz, who believes the data may have dozens of excellent leads for other researchers. "Our analysis only scratches the surface." The collaborating laboratories have placed the raw data from the study on Brown's Web site at <http://cmgm.stanford.edu/pbrown/sporulation>. "This information is out there for everybody to use," says Herskowitz.

Brown sees a variety of implications in this study. Chips coated with the full genome of an organism will most likely prove tremendously useful for studies of developmental pathways, says Brown. The approach might well be applied to study other developmental processes beyond germ cell production. If there is an ordered process, then the timing of gene expression should make it possible to identify potential regulatory sites in the pathway.