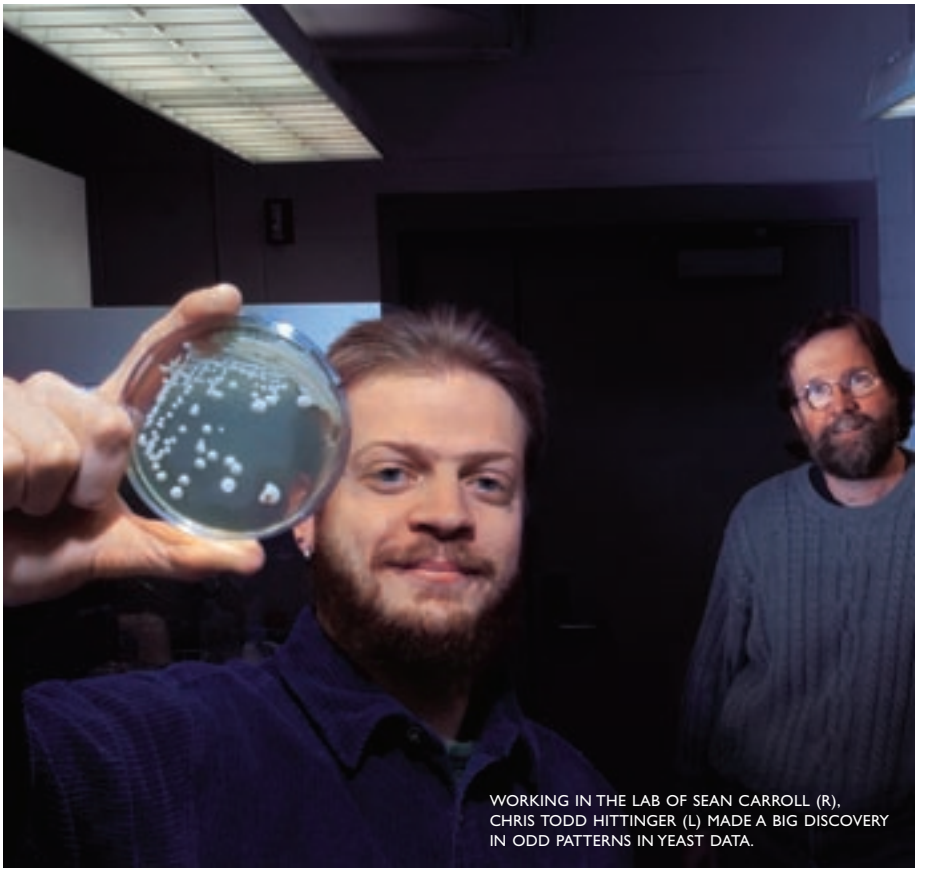
Fossil Genes: Another Gift from Yeast

Remnants of genes that fell into disuse offer clues on the process of natural selection.



DAVID NEVALA

WORKING IN THE LAB OF SEAN CARROLL (R), CHRIS TODD HITTINGER (L) MADE A BIG DISCOVERY IN ODD PATTERNS IN YEAST DATA.

THE BIG PICTURE

Chris Todd Hittinger's yeast finding is the latest in a spate of recent papers that connect physical or physiological change in an organism to its genetic evolution. One 2004 paper, for example, related jaw development in primates to a mutation in a muscle gene. This growing body of "evolutionary genomics" has implications for understanding how agents of disease, such as those involved in AIDS, make themselves difficult for the host's body and medical caregivers to target. As the field develops, "We'll have a good feeling for how evolution proceeds at the molecular and genetic level," says Hittinger. "It will likely give researchers a better perspective on how organisms will respond to various treatment regimes."

FOR THE PAST FEW THOUSAND YEARS, YEAST HAS LIVED A LIFE OF service, fermenting fruits and grains into wine and beer and breathing height into bread. More recently, yeast answered the call of science, serving as a model for countless experiments in genetics, genomics, and molecular biology. But long before it was so tamed, *Saccharomyces cerevisiae* and its single-celled cousins lived in the wilds of soil and foliage, grubbing out an existence from whatever sugar sources they could find.

At some point in that ancient history, millions of years ago, a number of those organisms lost their tastes for particular types of sugar. And as the yeasts acquired new tastes, they proceeded down different evolutionary paths. That divergence is recorded in the yeast genome today, as HHMI predoctoral fellow Chris Todd Hittinger at the University of Wisconsin–Madison has discovered. He reported the tale of this genetic and evolutionary change in the September 28, 2004, issue of the *Proceedings of the National Academy of Sciences*, in a paper coauthored with postdoctoral fellow Antonis Rokas and HHMI investigator Sean B. Carroll.

Using a menagerie of species, Carroll's lab studies the evolution of animal form and the closely related question of how animals develop from a single cell. Hittinger came to the lab in late 2001 with a double major in chemistry and biology from Southeast Missouri State University. "I was particularly interested in molecular evolution," he says.

For his graduate work Hittinger has been studying *Hox* genes, a class of genes that play a crucial regulatory role in the development of fruit flies and other animals by turning whole networks of genes on and off. Given the wealth of genomic data on yeast, he went on to examine a yeast gene that plays a similar regulatory role. The gene turns on the biochemical pathway that yeast uses to digest galactose, a common sugar that most organisms—from microbes to mammals—can consume. Galactose is an important component of mother's milk.

In searching the database of yeast genomes for the regulatory gene, "I noticed an odd pattern," says Hittinger. The gene was present in some, but not all, yeast species. He thought at first that this was a fluke of the data, so he dug further. Hittinger then found one species, *Saccharomyces kudriavzevii*, that retained the outline not only of the regulatory gene in question but of all seven genes in the galactose pathway. These genes were literally full of holes and other markers, however, indicating that they were nonfunctional: some DNA bases were missing, or the code contained "stop" instructions in the middle of the sequence rather than at the end. Without these genes intact, the yeast lacked the machinery to consume galactose—it had in essence lost its taste for the sugar.

Hittinger took his observations to Carroll, who remembers saying, "Write the paper!" What Hittinger had found was a

set of skeletal, or fossil, genes. "I could immediately tell him," says Carroll, "that this was a big story—a remarkable case of seven functionally related genes all in the process of decay."

Hittinger went back to the lab bench to sequence the genes in yeasts where data were incomplete. He and Rokas then pieced together a yeast family tree indicating that the ability to consume galactose was lost at least three separate times in yeast evolution. "Each one of the lineages found itself in a niche where galactose was less important for its survival," says Hittinger. In the case of *S. kudriavzevii*, which exists in the wild today only in Japan, the researchers note that it also has the unusual ability to consume a complex plant compound called inulin. They speculate that the yeast may have abandoned galactose as it acquired the specialized physiology to exploit a food source that few other organisms have the biochemistry to use. The remnants of the galactose pathway, however, can still be detected as the genes go through the evolutionary process of disappearing.

"It's such a signature of the way natural selection works," says Carroll. "It's use-it-or-lose-it. These genes fell into disuse, and they're being eroded like fossils on a shoreline." ■

~ Christine Mlot ~

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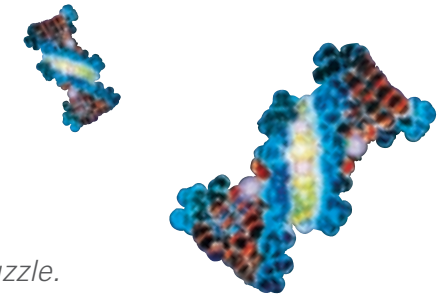

Modeling the Early Steps of DNA Processing

Scientist-educators—and students—join forces to solve a scientific puzzle.

TWO HEADS AND THREE TOOLS ARE sometimes better than one. An HHMI professor and a colleague who mentor HHMI-supported undergraduates are using the tools of molecular biology, biochemistry, and biophysics to solve a scientific puzzle.

What has their attention is the mysterious mechanism that enables DNA replication in simian virus 40 (SV40), a mammalian model for that vital process. "We've taken what began as a biochemical and molecular genetic approach, then used structural biology to learn about protein interactions, and then returned to biochemistry to validate our structural model in a functional way," said Ellen Fanning, an HHMI professor at Vanderbilt University, in Nashville, Tennessee.

Fanning and Walter Chazin, director of Vanderbilt's Center for Structural Biology, reported their findings in the April 2005 issue of *Nature Structural & Molecular Biology*, published online March 27, 2005.

The scientists sought the mechanism by which single-stranded DNA (ssDNA) breaks free from the chains of its binding protein to allow repair or replication, a process that is not well understood. Fanning and Chazin found structural and biochemical evidence for that mechanism, providing a model of this early step in DNA processing in mammalian cells.

Every organism has an ssDNA-binding protein for DNA replication and repair pathways. In eukaryotes (organisms whose cells have a nucleus), it is called replication protein A (RPA). One of the common functions of RPA in DNA processing pathways is facilitating "hand-off," a process that ensures that the correct proteins move into place along the ssDNA to begin DNA processing.

RPA plays an important protective role for ssDNA. RPA binds with at least a dozen different repair and replication proteins. The question has been how RPA gets dislodged, allowing various enzymes access to the DNA for necessary processing.

Using SV40 as a model system, the scientists mapped atomic-level interaction on the surfaces of proteins involved in DNA processing. They used biochemical and genetic tools to determine how the interactions of those proteins promote synthesis of small segments of RNA known as primers, which are required for initiation of DNA replication.

"This provides a testable model for how the ssDNA-binding protein can be displaced from single-stranded DNA to allow a DNA processing pathway," Fanning said. "This is a general phenomenon that happens throughout all DNA processing pathways." ■

~ Cori Vanchieri ~