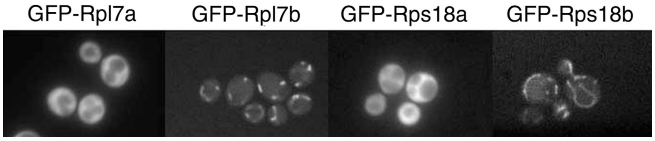
Research Roundup

Unique tasks for ribosomal paralogues

Long dismissed as molecular understudies, the duplicate ribosomal proteins in yeast actually perform unique functions, say Suzanne Komili, Pamela Silver (Harvard Medical School, Boston, MA), and colleagues. The findings suggest that yeast customize ribosomes for particular tasks.

Yeast harbor numerous duplicate genes. For example, 59 of their 78 ribosomal proteins have doubles that differ by only a few amino acids. For more than a decade, researchers thought that these paralogues were interchangeable, in part because knockouts showed no slowing of growth. However, recent work suggested that some so-called backups can't substitute for their counterparts, prompting Komili and colleagues to ask whether duplicate ribosomal proteins have distinct jobs during translation.

The team found that translation of the protein ASH1 went awry in strains lacking certain paralogues, suggesting that these copies were essential for regulating protein synthesis. Loss of paralogues also had broader, often contrasting effects on cell activities. Yeast missing the protein Rpl12a cranked up amino acid metabolism genes, for instance, whereas cells lacking its twin, Rpl12b, shut down genes involved in building the cell wall.



SILVER/ELSEVIER

Ribosomal paralogues (white) are not redundant, as shown by the faulty localization of only one of each pair in this mutant yeast line.

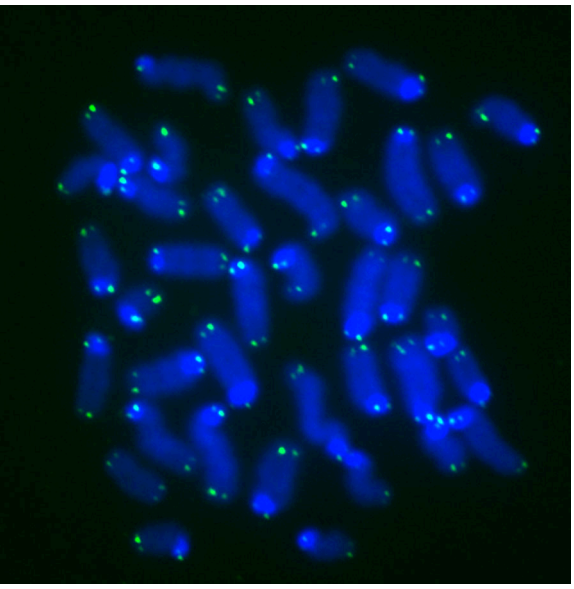
"The absence of one copy of a duplicated gene has a very different effect on the cell than the absence of the other copy of the same gene," says Komili.

Using information from databases and the literature, the team organized ribosomal paralogues by function. They found that the proteins didn't form set teams, in which the same paralogues always collaborate, but instead had shifting lineups. That result suggests that cells build specialized ribosomes, each carrying a different set of paralogues, that perform all the translation required for a certain function, such as spore formation. Other organisms, including humans, have duplicate ribosomal proteins and might show a similar specialization. JCB

Reference: Komili, S., et al. 2007. *Cell.* 131:557–571.

Embryonic telomeres go long

Telomeres go through a growth spurt early in embryonic development, as Lin Liu, David Keefe (University of South Florida, Tampa, FL), and colleagues report. The surge might help restore telomeres whittled down during oocytes' long quiescence.



KEEFE/MACMILLAN

The swapping of sister chromatid tips (green) in a one-celled embryo may lengthen telomeres.

Size is no issue for sperm, which maintain lengthy telomeres, and researchers assumed that eggs did the same. However, mammalian oocytes stall in meiosis, and for months or years they are besieged by reactive oxygen species that could wear down their telomeres. Supporting that idea, Keefe and coworkers recently reported that human oocytes have short telomeres. The researchers wanted to determine how these structures regrew.

Chromosome caps that were puny in mouse oocytes had stretched dramatically by the two-cell embryo stage, the team found. The stimulus for this growth didn't come from the sperm, because telomeres extended even in oocytes coaxed to develop parthenogenetically.

In stem cells and cancer cells, the enzyme telomerase keeps telomeres luxuriant. However, telomerase contributed little to embryonic elongation, the researchers discovered. Not only was telomerase activity low in oocytes and early embryos, but the chromosome tips grew nearly as long in cells that lack the enzyme as in wild-type cells. "Even with no telomerase activity, we saw lengthening of the telomeres during early development," says Keefe.

Elongation of the embryo telomeres might instead involve recombination between the tips of sister chromatids. The amount of swapping between telomeres shot up in early embryonic cells. Moreover, two DNA repair proteins—Rad50 and BLM—clustered in the nuclei of early embryos, suggesting that they could be mending telomeres after recombination.

The work indicates that early embryos rapidly extend their shrunken telomeres mainly through recombination. By the blastocyst stage, telomerase kicks in and finishes the job. Embryos might use recombination early on because telomerase can't add large stretches of nucleotides, Keefe says. JCB

Reference: Liu, L., et al. 2007. *Nat. Cell Biol.* doi:10.1038/ncb1664.

Text by Mitch Leslie
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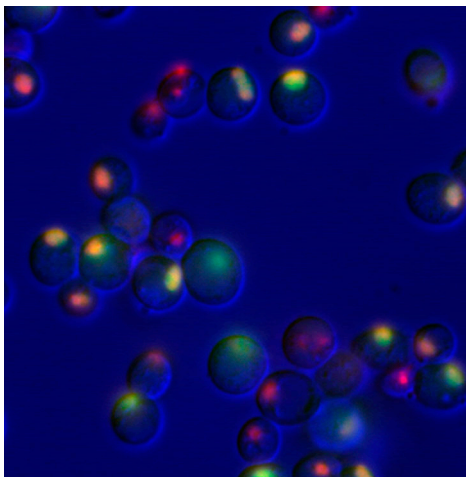


RAMANATHAN

Yeast on their way to meiosis start manufacturing Dmc1 (yellow).

Time to split

A yeast cell can stand out from the crowd by hastening or delaying meiosis. A yeast master regulator protein helps cells determine when to enter meiosis, as Iftach Nachman, Aviv Regev, and Sharad Ramanathan (Harvard University, Cambridge, MA) report.

Starvation spurs yeast to begin meiosis. But the process is complicated and irreversible, and cells that start too early or too late are at a disadvantage. To determine how yeast decide when to enter meiosis, the researchers cut rations for about 4,000 cells and tracked their progress.

Although the cells were genetically identical, they required anywhere between 7 and 17 hours to reach the first meiotic division. Much of this variability stemmed from the protein Ime1, which activates other meiosis-promoting proteins such as Dmc1. Ime1 production commenced shortly after the beginning of starvation and built up at a constant rate within an individual cell. But the protein's accumulation varied from cell to cell, explaining why cells entered meiosis on different schedules.

A yeast's position in the cell cycle had no effect on meiotic timing. Cell size had an influence, but further analysis indicated that size acted through Ime1. The work suggests that Ime1 is a meiosis timer. Like the countdown to a rocket launch, Ime1's count-up might allow cells to abort entry into meiosis if conditions change. JCB

Reference: Nachman, I., et al. 2007. *Cell.* 131:544–556.

RNA polymerase caught loitering

Instead of transcribing an entire gene, RNA polymerase sometimes starts to work and then pauses, finishing the job at a later time. According to a pair of papers, this herky-jerky transcription pattern affects more than 10% of fly genes, including some developmental movers and shapers.

That polymerase stalling occurs on a few genes is old news. However, no one had surveyed the entire genome to determine its prevalence. The two groups used chromatin immunoprecipitation microarrays to detect genes with polymerase stuck near the promoter.

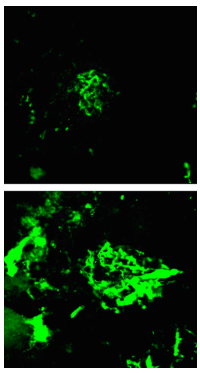
When Ginger Muse, Karen Adelman (National Institute of Environmental Health Sciences, Research Triangle Park, NC), and colleagues applied the technique to a line of embryonic *Drosophila* cells, they pinpointed stalling on more than 1,000 genes. Many were involved in development or responses to environmental stimuli.

Julia Zeitlinger, Michael Levine (University of California, Berkeley), and colleagues also identified lots of genes with idling polymerase in fly embryos. The list of 1,600 genes, which overlapped with that of the other group, included some architects of development, such as Hox, Wnt, and Notch. Having RNA polymerase poised for action might speed synthesis of needed proteins, help coordinate gene expression, or prepare genes for later activation. And the commonness of this effect "opens the door to a whole new cast of characters in regulating developmental genes," says Levine. JCB

References: Muse, G.W., et al. 2007. *Nat. Genet.* doi:10.1038/ng.2007.21.
Zeitlinger, J., et al. 2007. *Nat. Genet.* doi:10.1038/ng.2007.26.

Blinded by old macrophages

As they age, some cells simply fail to perform their jobs, but macrophages become troublemakers. According to Jennifer Kelly, Rajendra Apte (Washington University, St. Louis, MO), and colleagues, old macrophages promote abnormal blood vessel growth that can lead to diseases such as age-related macular degeneration (AMD).



APTE

Fewer abnormal blood vessels (green) grow beneath the retina after injections of young macrophages (top) than old cells (bottom).

Ample evidence suggests that macrophages check angiogenesis. Apte and colleagues previously reported that macrophages with Fas ligand (FasL) on their surface spur blood vessel cells to commit suicide, thus pruning new capillaries. But other work indicates that macrophages encourage vessel growth. The researchers wanted to pin down macrophages' effects on angiogenesis during AMD.

The team replicated AMD's key defect—growth of numerous vessels beneath the retina—by zapping the eyes of mice with a laser. Fewer vessels sprouted in young mice than in old animals. Injecting macrophages from young mice into the eyes of older mice curtailed angiogenesis, but macrophages from elderly mice didn't. Older macrophages underwent a character change, altering their cytokine output and producing less FasL. The trigger might be a surge in a known provoker of angiogenesis, interleukin-10.

The aging switch that transforms macrophages from angiogenesis blockers into angiogenesis boosters might contribute to other diseases with overactive vessel growth, including atherosclerosis and cancer. JCB

Reference: Kelly, J., et al. 2007. *J. Clin. Invest.* 117:3421–3426.