The secret of cell growth could be in 'yo-yo' and 'gear-like' tendencies

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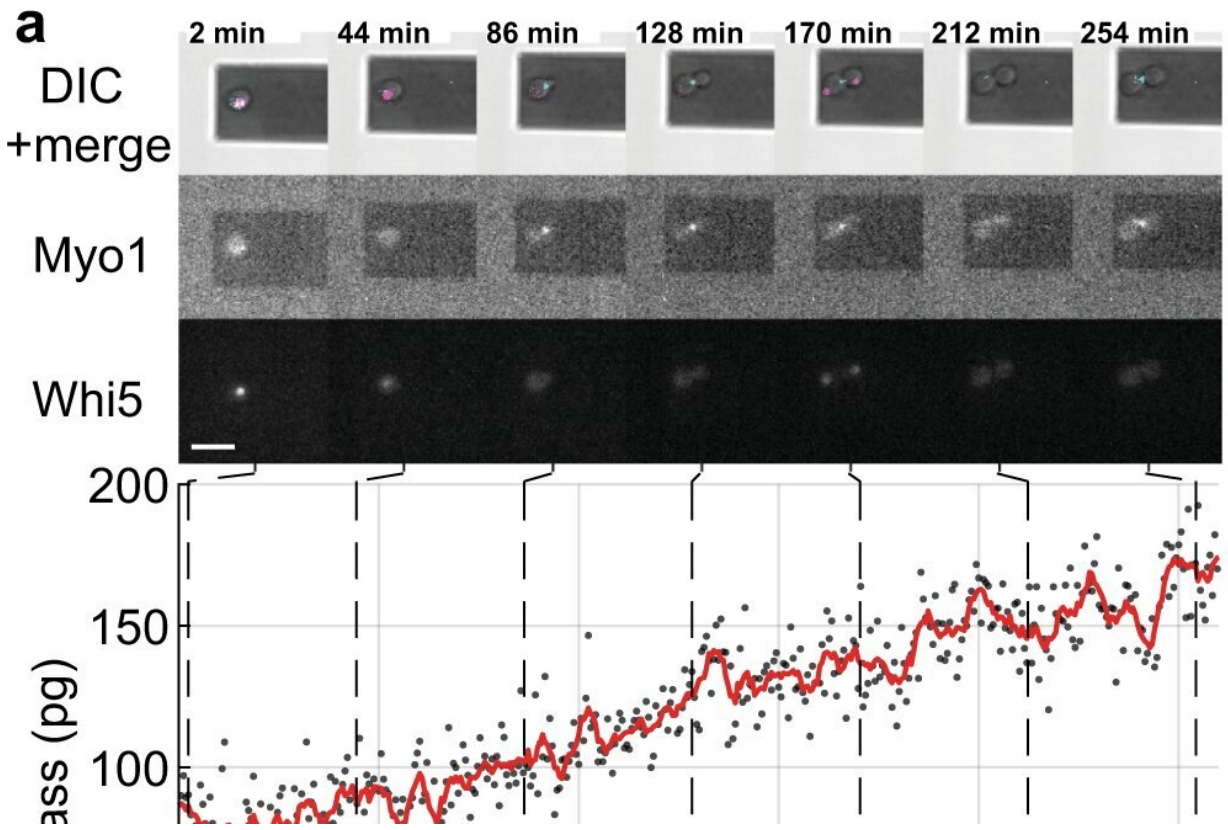

Mass and cell cycle measurements of single S. cerevisiae cells budding daughter cells. a, b Single yeast cells expressing the fluorescently labeled cell cycle marker proteins (Myo1-mKate2 (3×) and Whi5-mKOκ (1×)), were imaged using differential interference contrast (DIC) and fluorescence microscopy every 2 min (upper panels). A phase and amplitude curve of the microcantilever were recorded over intervals ≈50 s to measure the cell mass using the sweep mode (Supplementary Movie 4). Between consecutive mass measurements, the infrared and blue lasers of the picobalance were switched off for ≈ 20 s to

reduce bleaching of the fluorophores and to reduce potential perturbance of yeast growth. Cell mass values as derived from sets of single amplitude curves are shown as gray dots. Average raw data (350 s moving window, red line) shows the trend. Cyan bars on the time axis denote the S/G2/M phase of the yeast cell cycle, and magenta bars denote the G1 phase. The star (*) in b denotes the (partial) detachment of the daughter cell after cytokinesis, which drops the total mass. Scale bars (white), 10 µm. c Growth curves of (n = 19) single yeast cells progressing through the S/G2/M phase (bud growth) as measured by the picobalance using the sweep mode in (n = 19) independent experiments. The overall growth rates between starting and end mass range between 0.1 and 2.0 pg min^{-1}, with an average of 0.7 ± 0.5 pg min^{-1} (mean ± SD). The duration of the S/G2/M phase ranges from 57 to 184 min, with an average of 96 ± 35 min. Credit: *Nature Communications* (2022). DOI: 10.1038/s41467-022-30781-y

Cells, the most basic units of life that form all living organisms, have long guarded their secrets, but now an international team from the University of Sydney, ETH Zurich and the University of Basel has uncovered some of their secrets through the development of a world-first technique.

Scientists know that cells grow but it was commonly thought that they grow linearly or exponentially in size, before dividing.

Now, in a paper published in *Nature Communications* co-led by University of Sydney physicist Dr. David Martinez-Martin, using a nanotechnology technique called "inertial picobalance," scientists have identified that at the single cell level, yeast grow in sequential intervals or segments of linear growth (constant growth rate). At each interval, yeast cells switch to faster or slower growth—a "gear-like" tendency.

The research was performed with saccharomyces cerevisiae, a unicellular yeast organism fundamental in the production of bread, beer,

wine and pharmaceuticals. The protein-encoding genes of many types of yeast mirror genes in animal cells, making its behavior key to understanding human disease.

Notably, the behavior found in yeast differs significantly from that of animal cells (including human). It was not until 2017 that Dr. Martinez-Martin and colleagues, also using picobalance, first observed that the mass of living mammalian cells fluctuate intrinsically—they "yo-yo" in size.

"We have uncovered processes that challenge models in biology that have been central for decades," said Dr. Martinez-Martin. "The behaviors we have identified in cells from fungus and animal kingdoms provide strong evidence that cells have different strategies to regulate their mass and size, paving the way to better understand how they can accurately form and reform complex structures such as the eyes, brain and fingers in our bodies."

A recent mathematical model published in *Journal of Biological Research—Thessaloniki* by Dr. Martinez-Martin also offers fresh insight into the meaning of this once-secretive cellular flux.

"Another of our recent studies has found that while cell mass fluctuations have been detected in single mammalian cells, they can be perfectly viable in organisms comprised of many mammalian cells, including humans. Our modeling suggests that the body's cells don't all swell and decrease at the same time—instead they give and take from each other, maintaining an adequate distribution of the body's mass and volume.

"Mass fluctuations may be used by cells to regulate cellular functions such as metabolism, gene expression, proliferation and cell death, by means of altering the concentration and crowdedness of chemical

cellular components."

The model also suggests that mass fluctuations allow cells to communicate, both by acting as biomechanical signals through volume fluctuations, and through the exchange of water and molecules.

"I believe this could be a fundamental mechanism which may help cells locate and communicate their position within an organism," Dr. Martinez-Martin said. "Therefore, it could be incredibly important, because it could allow cells to identify and serve their distinct role and purpose in the body."

"Researchers believe that a better understanding of how cells change their mass and size over time, as well as dysregulation of this process (when cells change their size atypically), could be the key to developing the next generation of diagnostics and treatments for a range of diseases, such as cancer, diabetes and cardiovascular disease."

About inertial picobalance: The technique used in the discovery

Dr. Martinez-Martin, who has been recently distinguished by the World Intellectual Property Organization as a young change maker, is the principal inventor of inertial picobalance, a new technology that measures the mass of single or multiple living cells in real-time, enhancing the understanding of cell physiology. The technology is currently being commercialized by the Swiss nanotech company, Nanosurf AG.

In a *Nature* paper published in 2017, using inertial picoblance, Dr. Martinez-Martin and his colleagues discovered that the mass of living mammalian cells fluctuates intrinsically by one to four percent over

seconds, largely due to water entering and exiting cells.

Using this technique, they were also able to observe cells infected with the vaccinia virus (a virus from the poxvirus family). The infected cells showed different mass behavior over time than non-infected cells, potentially enabling a new way of detecting viral infections.

More information: Andreas P. Cuny et al, High-resolution mass measurements of single budding yeast reveal linear growth segments, *Nature Communications* (2022). DOI: 10.1038/s41467-022-30781-y

Provided by University of Sydney