LAB-ON-A-CHIP

The age of yeast

A simple microfluidic device allows long-term imaging of single budding yeast cells.

Each of us has intimate experience with aging, yet we understand it poorly. In great introspective self-portraits that spanned his artistic life, Rembrandt showed the importance of documenting the aging process in order to comprehend it. To ask more basic questions, researchers have turned to watching single cells age, often in simple organisms such as budding yeast. The problem is that following single yeast cells requires technology that—though newer than oil paint and canvas—can be tedious to use. Matthias Heinemann and colleagues at the University of Groningen and ETH Zurich have now developed a simple automated way to observe yeast cells as they age and die.

Cells are thought to age from a combination of environmental insults that cause cellular damage and an intrinsic genetic program. Budding yeast has some genetic aging pathways in common with other cells, including mammalian cells, and responds similarly to nutrient restriction by extending its life. (Elderly yeast have wrinkles, too.) As yeast cells are quickly overwhelmed in number by their progeny, daughter cells typically needed to be laboriously picked away by a needle to study aging. This required a long-working-distance objective with limited resolution or fluorescence capability.

Heinemann and his colleagues were not thinking of these problems when they came up with a solution. "We first wanted to have a microfluidic device where we could look into the growth of single cells and change the environment of those cells," says Heinemann. It worked so well that they could follow cells throughout their replicative lifespan.

Their device exploits a simple feature that distinguishes mother and daughter cells—their size. Yeast cells are first flooded into the device, which is made from a soft elastomer pad that traps the larger mother cells against a microscope cover slip. A constant flow of controlled medium then ensures that smaller cells that bud off the mother cells are washed away. Arrays of micropads trap large numbers of cells in a single experiment.

The setup allows almost any aspect of yeast biology, as well as the effect of environmental changes, to be monitored dynamically throughout a cell's lifespan, with the critical advantages of increased throughput and resolution. It does not have the problem of local resource depletion or by-product accumulation common to other automated monitoring methods. Using the chip, the researchers found that yeast cells face death in different ways: one group meeting their end as spheres, relatively young, and another as ellipsoids. "There is probably not only one pathway to death, so that you will see heterogeneity as cells age," observes Heinemann.

Following single cells through all the budding events from youth to death will help to dissect this heterogeneity, and will be useful for the study of yeast cell cycle. Although the age of cells loaded into the device is unknown, the authors estimate that the vast majority of mother cells have not produced any offspring at the time of trapping. Daughter cells also cannot be followed except in cases where they fortuitously stay attached for some time to the mother cell.

Researchers who do not regularly deal with microfluidics are often hesitant to use these types of devices, something that Heinemann understands. "I had my years of frustration with microfluidic work," he says. But given its simple design, he says that without any microfluidics experience, anyone can learn to make and use the chip in a few days, and it is very robust: nearly every chip works. The device can run by itself for days, allowing one venerable mother cell to be followed until it died at a record 65 cell cycles.

The ease of using such a chip should help to open up the yeast aging field, promising many new insights into an age-old problem.

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Lee, S.S. *et al.* Whole lifespan microscopic observation of budding yeast aging through a microfluidic dissection platform. *Proc. Natl. Acad. Sci. USA* **109**, 4916–4920 (2012).