Weighing the cell: Measuring, for the first time, how single cells accumulate mass (w/ Video)

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Using a sensor that weighs cells with unprecedented precision, MIT and Harvard researchers have measured the rate at which single cells accumulate mass -- a feat that could shed light on how cells control their growth and why those controls fail in cancer cells.

The research team, led by Scott Manalis, MIT associate professor of biological engineering, revealed that individual cells vary greatly in their growth rates, and also found evidence that cells grow exponentially (meaning they grow faster as they become larger).

The new measurement system, reported in the April 11 edition of the journal *Nature Methods*, is the first technique that can measure cells' mass as they grow over a period of time (in this case, ranging from five to 30 minutes). Previous methods for measuring cell growth rates have focused on volume or length measurements, and have not yet exhibited the necessary precision for revealing single-cell growth models.

The new method should give researchers a way to unravel the relationship between cell growth and cell division — a relationship that has long been murky, says Marc Kirschner, professor of systems biology at Harvard Medical School. While biologists have a good idea of how the cell division cycle is controlled, "the problem of cell growth — how a cell regulates the amount of material it makes — is not well known at all," says Kirschner, an author of the Nature Methods paper.

Controlled growth

A longstanding question in studies of cell growth is whether growth is linear or exponential. Previous studies have yielded conflicting data.

“Over the twofold size range experienced by most proliferating cells, linear and exponential growth curves differ by less than 10 percent, and so the measurement precision must be much less than this,” says Manalis, a member of MIT’s David H. Koch Institute for Integrative Cancer Research.

The researchers studied four types of cells: two strains of bacteria (E. coli and B. subtilis), a strain of yeast and mammalian lymphoblasts (precursors to white blood cells). They showed that B. subtilis cells appear to grow exponentially, but they did not obtain conclusive evidence for E. coli. That’s because there is so much variation between individual cell growth rates in E. coli, even for cells of similar mass, says Francisco Delgado, a grad student in Manalis’ lab and co-lead author of the paper.

If cells do grow exponentially, it means there must be some kind of mechanism to control that growth, says Kirschner. Otherwise, when cells divide into two slightly different-sized daughter cells, as they often do, the larger cell in each generation would always grow faster than the smaller cell, leading to inconsistent cell sizes. Instead, cells generally even out in size, through a mechanism that biologists don’t yet understand.

Going with the flow

The cell-mass sensor, which Manalis first demonstrated in 2007, consists

of a fluid-filled microchannel etched in a tiny silicon slab that vibrates inside a vacuum. As cells flow through the channel, one at a time, their mass slightly alters the slab's vibration frequency. The mass of the cell can be calculated from that change in frequency, with a resolution as low as a femtogram (10-15 grams) which is less than 0.01 percent of the weight of a lymphoblast cell in solution.

Michel Godin, a former postdoctoral associate in Manalis' lab and co-lead author of the paper, developed a way to trap a cell within the microchannel by precisely coordinating the flow direction. That enables the researchers to repeatedly pass a single cell through the channel every second or so, measuring it each time it moves through.

The new system represents a significant advance over any existing cell measurement technique, says Fred Cross, a Rockefeller University professor who studies the yeast cell cycle. "Since it directly measures biomass (at least net biomass with density greater than water) by the truly remarkable expedient of effectively directly placing a single cell on a scale, it is not troubled by ambiguities and inaccuracies inevitably associated with previous, more indirect measurements," Cross says.

In their current studies, Manalis and his students are tagging proteins inside the cell with fluorescent molecules that reveal what stage of the cell cycle the cell is in, allowing them to correlate cell size with cell-cycle position and ultimately obtain a growth model for yeast and mammalian cells. They are also working on a way to add chemicals such as nutrients, antibiotics and cancer drugs to the fluid inside the microchannel so their effect on growth rates can be studied.

More information: "Using buoyant mass to measure the growth of single cells," Michel Godin, Francisco Feijo Delgado, Sungmin Son, William Glover, Andrea Bryan, Amit Tzur, Paul Jorgensen, Kris Payer, Alan Grossman, Marc Kirschner and Scott Manalis. *Nature Methods*,

April 11, 2010.

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