Sizing cells up: Researchers pinpoint when a cell is ready to reproduce

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For more than 100 years, scientists have tried to figure out the cell size problem: How does a cell know when it is big enough to divide? In research conducted in budding yeast (Saccharomyces cerevisiae), scientists at Rockefeller University have now identified the cellular event that marks the moment when a cell knows it is big enough to commit to cell division and spawn genetic replicas of itself. The findings provide a precise and quantitative framework for studying the possible mechanisms that allow cells to monitor and sense their size.

During the first phase of the cell cycle, known as G1, budding yeast grows and begins to form a bud; in the final stage, the cell splits into two — one bigger than the other. Although researchers have identified several key proteins that regulate and play a role in coordinating cell growth and division during G1, they have not been able to get to the core mechanism that senses whether a cell possesses enough resources to divide. Scientists needed a way to organize and confidently sort out molecular candidates involved in cell size control from those that played other roles.

Graduate student Stefano Di Talia, a biophysicist, and postdoc Jan Skotheim, an applied mathematician, provided just that. Working with Eric Siggia, head of the Laboratory of Theoretical Condensed Matter Physics, and Fred Cross, head of the Laboratory of Yeast Molecular Genetics, Di Talia and Skotheim showed that a unique cellular event, the exiting of the protein Whi5 from the nucleus, separates G1 into two independent steps: one controlled by a sizer (T1) and one controlled by a

timer (T2). T1 begins when the mother and daughter cells have completely separated from each other; T2 starts in G1 once Whi5 has exited the nucleus and lasts until the new daughter cell forms its own bud.

“You need some way to know how big you are,” says first author Di Talia, whose work appears in the August 23 issue of Nature. “This precise quantitative framework allows us to narrow down the possibility of events that are involved in size control.”

By measuring the sizes of budding yeast and how long they spend in G1 and in T1, Di Talia saw that daughter cells, which are much smaller than their mother cells, need to spend more time in T1 growing. Once daughter cells reach the required size for division, they spend as much time as their mothers in T2, subsequently replicating their DNA and producing daughter cells of their own. Di Talia and his colleagues used genetics to show that a different medley of proteins coordinate cell growth and division during T1 and T2, a crucial finding highlighting that these two parts of G1 are independent from each other and are regulated by different mechanisms.

“If we continue to identify the molecular events that change how T1 is regulated,” says Di Talia, “we can really hope to get to the core of what the size-sensing machinery is.”

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