Checkered history of mother and daughter cells explains cell cycle differences (w/ Video)

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When mother and daughter cells are created each time a cell divides, they are not exactly alike. They have the same set of genes, but differ in the way they regulate them. New research now reveals that these regulatory differences between mother and daughter cells are directly linked to how they prepare for their next split. The work, a collaboration between scientists at Rockefeller University and the State University of New York, Stony Brook, may ultimately lead to a better understanding of how cell division goes awry in different types of cancer. The findings are reported in this week's *PLoS Biology*.

"You can basically think of mother and daughter cells as different cells just like you would a neuron and liver cell but on a much subtler level," says first author Stefano Di Talia, who received his Ph.D. from Rockefeller in 2009. "We found that their differences in gene expression are also what makes the mother and daughter cells start their cell cycles differently."

When a mature cell divides, it produces a mother and a daughter cell, the daughter being smaller than the mother, explains Di Talia, who is now a postdoc at Princeton University. Since the 1970s, it was thought that both mother and daughter cells use the same gears and levers to prepare for cell division. The only difference was that the daughter cell would take longer to start dividing on account of its size.

This tidy explanation now gives way to a more nuanced version, the seeds of which can be traced to research from the University of

Wisconsin in 2003. It was then proposed that the size of the daughter cell has no bearing on whether it is ready to divide. What matters is that the daughter cell, and not the mother cell, receives a protein called Ace2 at the time the two cells are born. "This model was against the accepted dogma and against our own previous findings. Our work was an attempt to resolve the debate," says Di Talia.

Di Talia and Frederick R. Cross, head of Rockefeller's Laboratory of Yeast Molecular Genetics and a researcher who, like the Wisconsin group, works with budding yeast, seem to have reconciled the two theories and in the process nailed down new details.

The researchers found that both mothers and daughters do control and sense their size before committing to divide but the levers and gears that they use to make that commitment are different. The reason: Daughters, but not mothers, receive the protein Ace2 as well as a never-before-implicated protein called Ash1, which, like Ace2, controls the levers that crank genes into gear.

In their work, Di Talia and Cross studied a phase of the cell cycle known as G1, during which cells determine whether they are healthy enough to enter another grueling phase of division. G1 is considered critical because mistakes in this process can lead to cancer.

Di Talia and Cross, with colleagues Bruce Futcher and Hongyin Wang at SUNY Stony Brook, found that daughter cells, which normally have Ace2 and Ash1, interpret their size as 20 percent smaller than their birth twin. The researchers show that, without these proteins, daughter cells begin dividing as if they were mother cells, even at a size that would normally be deemed too small. When Ace2 and Ash1 were genetically manipulated to localize into mothers as well, the opposite happened: they unnecessarily continued to grow and began dividing as if they were daughters.

This critical finding showed that the direct target of these two proteins is a gene called CLN3, which scientists have long suspected is the ultimate green light for cells to start dividing. The reason daughter cells spend a longer time preparing for cell division is because both Ace2 and Ash1 lower the expression of CLN3. To make sure daughter cells do not start dividing before they are ready, and as backup, Ace2 also turns on production of Ash1.

"This work builds on our previous findings very nicely," says Di Talia. "That CLN3 is the central regulator of this cell cycle phase and that it is controlled very precisely shows that even small changes can result in big differences."

Source: Rockefeller University (news : web)