Research Roundup

For cdks, one is enough

We can't turn sugars into a good pinot noir, but we do resemble yeast in one surprising way. Like the fungi, mammals require only one cyclin-dependent kinase (cdk) to complete the cell cycle, say David Santamaria, Mariano Barbacid (Spanish National Cancer Research Center, Madrid, Spain), and colleagues.

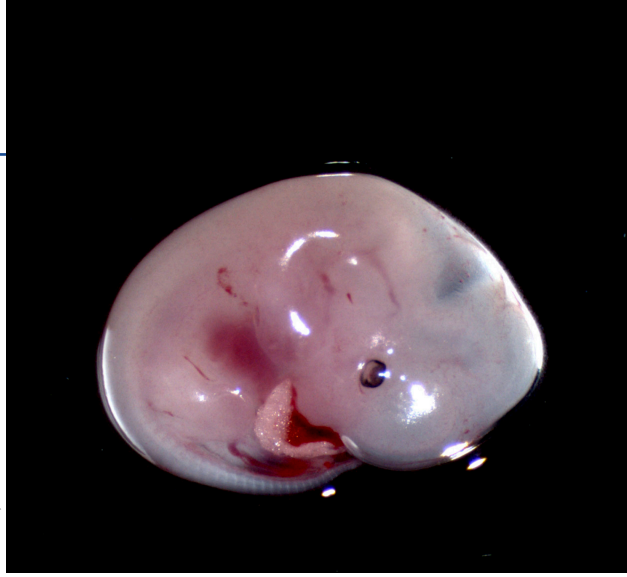
Although yeast need only one cdk to turn the cell cycle, the standard view was that mammals depend on at least five. Cdk2, Cdk3, Cdk4, and Cdk6 push the cell through interphase, whereas Cdk1 nudges it into mitosis. However, recent studies suggest otherwise. For example, lab mice are missing Cdk3 due to a mutation, and they show developmental—but not cell cycle—defects if they also lack any other pair of cdks.

To find out whether one cdk can suffice in mammals, the researchers analyzed mouse embryos that only manufactured Cdk1. The animals appeared to develop normally until they were about 13 days old, when their liver cells began dying en masse. The animals failed to produce enough hematopoetic cells, and the heart wall was weak. The mice died, but they managed to pull off about 20 million cell divisions, suggesting that Cdk1 alone can propel the cell cycle. In vitro studies confirmed the finding. Fibroblasts from the embryos proliferated in culture, albeit slowly.

Although Cdk1 can drive the cell cycle without the other cdks, the reverse is not true. Cdk1 is crucial for the earliest steps of development, as the researchers showed by crossing animals that had only one working copy of the Cdk1 gene. Homozygous embryos without Cdk1 did not survive past the morula stage.

"The classical model [of cdk action] can't be sustained," says Barbacid. However, the results don't mean that the other cdks are dispensable, he notes. They are essential for division in specific cell types, such as hematopoetic cells and cardiac muscle. The researchers now want to cross cdk knockout mice with cancer-prone mice to determine which of the proteins are essential for tumor growth. JCB

Reference: Santamaria, D., et al. 2007. *Nature*. 448:811–815.



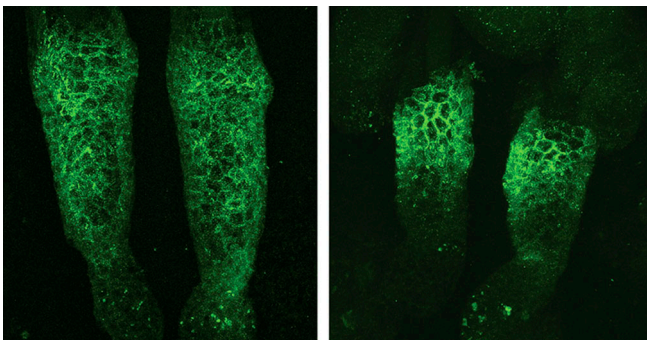
BARBACID/MACMILLAN

Cells still cycle in an embryo with only Cdk1.

Wnt makes stem cells act their age

The Wnt pathway helps embryos get into shape, but its continued activation during adulthood saps the stem cells that refurbish tissues, according to two studies. The findings implicate Wnt in the stem cell failure that might be a cause of aging.

Both groups chanced on the connection to Wnt, whose many functions include promoting differentiation and cell division. Hongjun Liu, Toren Finkel (National Heart, Lung, and Blood Institute, Bethesda, MD), and colleagues were studying mice that lack the protein klotho. The animals die young after showing signs of premature aging such as hardened arteries. The researchers detected a surge in cellular senescence in locations where stem cells are proliferating, such as the skin, small intestine, and bone marrow.



FINKEL/AAAS

The bulge region of a hair follicle is normally packed with stem cells (left), but the cells are scarce if klotho is absent (right).

Klotho and Wnt proteins are antagonists, the scientists found. Adding klotho to cultured cells quashed Wnt activity. Moreover, Wnt pushed mouse embryonic fibroblasts to senesce, but extra klotho countered the effect. Overall, the work indicates that, by boosting senescence, Wnt spurs animals to fritter away their stem cells.

Andrew Brack, Tom Rando (Stanford University, Stanford, CA), and colleagues report similar results for satellite cells. These cells normally mend damaged muscle, but as we get older, they often start producing tough fibers instead of fresh muscle cells. Wnt spurs other cell types to morph into fiber-manufacturing cells, and the researchers determined that the pathway did the same to muscle. Adding Wnt3A to young satellite cells, for example, caused more to convert into fiber makers.

The results held true in vivo. Injecting Wnt3A into injured muscles of young mice slowed cell division and boosted fiber formation. The scientists also found that, in older mice, Wnt signaling in satellite cells climbed. The findings suggest that Wnt undermines our muscles' capacity for repair as we age. JCB

References: Liu, H., et al. 2007. *Science*. 317:803–806.
Brack, A.S., et al. 2007. *Science*. 317:807–810.

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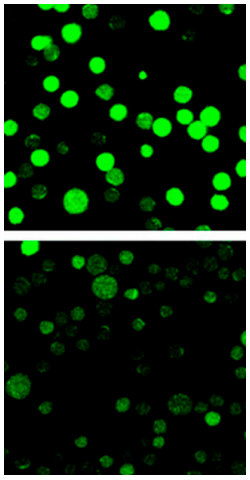


THOMPSON/ELSEVIER

Stimulating T cells boosts ROS production (top row), but not if Bak and Bax are absent (bottom row).

Apoptosis promoters spur cell division

Two cell-killing proteins also have a nurturing side, say Russell Jones, Craig Thompson (University of Pennsylvania, Philadelphia, PA), and colleagues. Although the proteins prod lymphocytes to commit suicide, they also prompt the cells to proliferate—and might do the same for a variety of cell types.

The two proteins, Bax and Bak, are part of the apoptotic machinery in T lymphocytes. Weeding out excess T cells turns down the immune response after a pathogen has been defeated. Mice that lack Bax and Bak in blood cells often fall victim to infections, suggesting that the two proteins are also involved in lymphocyte activation.

The researchers found that T cells missing Bak and Bax divided slowly after stimulation. Injecting bacteria into mice lacking both proteins in their lymphocytes didn't provoke a T cell response to the invaders. T cell activation involves a surge in intracellular calcium, but loss of Bax and Bak reduced this increase. The scientists discovered that rising calcium levels boosted production of reactive oxygen species (ROS) in the cell, which is essential for proliferation.

The work suggests that Bax and Bak rouse T cells in part by hiking ROS levels. These compounds can also kill cells, and the mechanism for adjusting ROS quantities to favor death or division remains uncertain. But Bax and Bak might regulate ROS production to awaken other quiescent cells, such as stem cells. JCB

Reference: Jones, R.G., et al. 2007. *Immunity*. 27:268–280.

Fusing without breaking

The same membrane rearrangements that prompt two cargo-carrying vesicles to unite can also provoke them to burst. Vincent Starari, Youngsoo Jun, and William Wickner (Dartmouth Medical School, Hanover, NH) explain how cells favor fusion over breakage.

Fusion between, say, the Golgi apparatus and a vesicle fresh from the ER requires a crew of molecules. The participants include Rab GTPases, Rab effectors that bind active Rab and transmit its signals, and SNARE proteins, which interlock to draw the opposing membranes together. Liposomes carrying SNAREs fuse in vitro, but recent studies revealed that many liposomes rupture, which doesn't happen in cells.

To investigate the cause of lysis, the authors observed purified yeast vacuoles, which merged without bursting. They then tracked vacuoles from yeast engineered to overexpress four SNARE proteins. Although some of the containers fused, up to 80% of them popped. "That's not like a little leak in the *Titanic*," says Wickner. "That's like ramming the iceberg." The findings explain why cells can't boost fusion by increasing the amount of SNAREs—rampant lysis would result.

In the vacuoles with extra SNAREs, fusion and lysis occurred without Rab GTPase. But Rab was beneficial because it increased the rate of fusion by several thousand times. The work thus also clarifies the functions of Rab GTPase and its partners: they channel the stress that the SNAREs apply to the membrane into fusion rather than lysis. JCB

Reference: Starari, V.J., et al. 2007. *Proc. Natl. Acad. Sci. USA*. 104:13551–13558.

The price of excess DNA

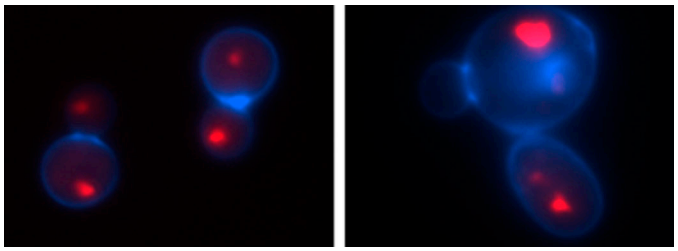
Aneupoloidy might not be a boon for cancer cells after all, say Eduardo Torres, Angelika Amon (Massachusetts Institute of Technology), and colleagues. Extra chromosome copies slow division, the researchers found.

Almost all tumors are aneuploid, and scientists have long suspected that the condition aids the renegade cells. Chromosome gain could provide extra copies of growth-promoting genes, and chromosome loss might jettison tumor suppressors. However, several studies, including work on cells from Down syndrome patients, suggest that aneuploidy inhibits cell proliferation.

To investigate aneuploidy's effects systematically, Torres and colleagues turned to mutant yeast that occasionally end up with spare chromosomes after mating. The researchers corralled cells that carried at least one extra copy of 13 of the yeast's 16 chromosomes. The fungi resembled cancer cells in their ravenous appetite for glucose.

But the yeast differed from cancer cells in a crucial way: they divided sluggishly. The reason for the slowdown was a tarry in G1. Although aneuploidy might be helpful in some circumstances, Amon says, cancer cells must get around the division limitation to reap the benefits. "What we're saying," she explains, "is that cells have to evolve pathways to deal with the baggage that comes with aneuploidy." JCB

Reference: Torres, E.M., et al. 2007. *Science*. 317:916–924.



TORRES

The yeast cells on the right harbor an extra copy of chromosome 4, which slows their division.