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Forever Young

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ductance may not be critical in neuronal death at a later stage of stroke (Liu et al., 2007). Furthermore, a number of studies have identified other signaling components downstream of NR2B required for excitotoxic/ischemia induced neuronal death, such as neuronal nitric oxide synthase (Aarts et al., 2002) and SREPB1 (Taghibiglou et al., 2009), and it will be important to identify how these tie into the findings of Tu et al.

Finally, it will also be interesting to explore the role of DAPK1 under physiological conditions. Its strong neuronal expression and localization in the post-synapse suggest a role in synaptic function yet to be discovered. Either way, the findings of Tu et al., along with several

other studies (Aarts et al., 2002; Taghibiglou et al., 2009), support the concept that targeting cell death signaling downstream of NMDARs is an effective neuroprotective strategy. In this regard, we very much share the hope with the authors that their discoveries might lead to new effective treatments for stroke.

REFERENCES

- Aarts, M., Liu, Y., Liu, L., Besshoh, S., Arundine, M., Gurd, J.W., Wang, Y.T., Salter, M.W., and Tymianski, M. (2002). *Science* 298, 846–850.
- Bayer, K.U., De Koninck, P., Leonard, A.S., Hell, J.W., and Schulman, H. (2001). *Nature* 411, 801–805.
- Bialik, S., and Kimchi, A. (2006). *Annu. Rev. Biochem.* 75, 189–210.
- Hardingham, G.E., Fukunaga, Y., and Bading, H. (2002). *Nat. Neurosci.* 5, 405–414.
- Lipton, S.A., and Rosenberg, P.A. (1994). *N. Engl. J. Med.* 330, 613–622.
- Liu, Y., Wong, T.P., Aarts, M., Rooyackers, A., Liu, L., Lai, T.W., Wu, D.C., Lu, J., Tymianski, M., Craig, A.M., and Wang, Y.T. (2007). *J. Neurosci.* 27, 2846–2857.
- Strack, S., McNeill, R.B., and Colbran, R.J. (2000). *J. Biol. Chem.* 275, 23798–23806.
- Taghibiglou, C., Martin, H.G., Lai, T.W., Cho, T., Prasad, S., Kojic, L., Lu, J., Liu, Y., Lo, E., Zhang, S., et al. (2009). *Nat. Med.* 15, 1399–1406.
- Tovar, K.R., and Westbrook, G.L. (2002). *Neuron* 34, 255–264.
- Tu, W., Xu, X., Peng, L., Zhong, X., Zhang, W., Soundarapandian, M.M., Balel, C., Wang, M., Jia, N., Zhang, W., et al. (2010). *Cell*, this issue.

Forever Young

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Propagation of a species requires periodic cell renewal to avoid clonal senescence. Liu et al. (2010) now describe a new mechanism of cell renewal in budding yeast, in which damaged protein aggregates are transported out of the daughter buds along actin cables to preserve youthfulness.

The separation of germ cells from the soma potentiates the propagation of a species that lacks senescence, because new mechanisms emerge to preserve youthfulness in the specialized germ cells (Weisman, 1892). In contrast, somatic cells age, at least in part, because they lack these mechanisms. The budding yeast provides a conceptual analog of the germ cell/somatic cell demarcation, because cells divide asymmetrically to give a young daughter cell that arises from the bud (the germ cell analog) and a mother cell that grows older with each budding event (the somatic cell analog). Studies by the Nystrom lab have shown that damaged protein aggregates accumulate in aging mother cells, but not in their daughters (Aguilaniu et al., 2003). Now, in this issue, Liu et al. (2010) uncover an exciting new mechanistic

basis for this asymmetry. They show that these damaged protein aggregates undergo retrograde transport along actin cables out of the growing bud and into the mother cell (Figure 1).

The path leading to this discovery was based on this group's earlier finding that the asymmetric segregation of damaged proteins between mother and daughter cells required the anti-aging gene *SIR2*. This gene encodes an NAD-dependent deacetylase that retards aging in organisms ranging from yeast to mammals (Finkel et al., 2009). In their new work, Liu et al. (2010) looked for new *SIR2* functions using synthetic gene arrays (Tong et al., 2004) to identify genes that are required for survival of *sir2* yeast mutants. Not surprisingly, one major category of genes was involved in the maintenance of chromatin. Less expected was the

large number of genes involved in actin-related cellular processes, including genes that encode components of the polarisome (Moseley and Goode, 2006). The polarisome is a structure located at the distal end of the yeast bud that forms a focal point for polymerization of actin monomers into cables that extend from the bud tip to the mother cell (Figure 1). These actin cables transport cargo from mother to daughter cell to support bud growth. This genetic association between a gene encoding a polarisome component and *SIR2* is specific as no such interactions were observed for the yeast *SIR2* paralog, *HST2*.

The authors identify a likely mechanistic link between Sir2p and the polarisome by analyzing actin itself. In *sir2* mutant strains, there is a substantial amount of unfolded actin monomers. In addition,

the chaperone involved in actin folding, CCT, is relatively inactive when purified from *sir2* mutants. Given that inactive CCT is also hyperacetylated, it seems likely that Sir2p deacetylates CCT to activate this chaperone, which then induces the correct folding of actin, thereby promoting the formation of actin cables at the polarisome. These biochemical findings are consistent with the phenotypes of the *sir2* mutant strains. Indeed, the ability of dividing cells to retain damaged proteins in mother cells was partially compromised in strains with mutations in polarisome components, and deletion of *SIR2* exacerbated this defect. Further, like *sir2* mutants, all of the polarisome mutants had a short replicative life span, with the exception of the *BUD6* mutant.

Most strikingly, the authors directly demonstrate retrograde transport of damaged proteins from buds to mother cells (Figure 1). Prior work showed that *SIR2* exerts its effect on the asymmetry of segregation of damaged proteins through the heat shock protein Hsp104 (Erjavec et al., 2007). Here, the authors used Hsp104 tagged with green fluorescent protein (GFP) to visualize aggregates induced by heat treatment, which are presumed to contain damaged proteins bound to Hsp104-GFP. Importantly, application of heat caused the immediate formation of aggregates in both the mother and the bud. However, the aggregates in the bud were transported back to the mother along actin cables, where they fused with a protein aggregate already present in the mother. This retrograde transport was compromised by mutation of Sir2p, polarisome proteins, or a component of the actin cable, tropomyosin.

What drives the retrograde movement of the damaged cargo from bud to mother? The motor protein Myo2p is required for forward movement of cargo from the mother to the bud during growth (Figure 1), but there is no evidence that this motor moves in a retrograde direction. The authors suggest that the polymerization of actin itself, which occurs at the polarisome and extends growing cables back toward the mother cell, may provide the directionality and force to move the damaged cargo resulting in a pristine bud. How the actin cables selectively bind

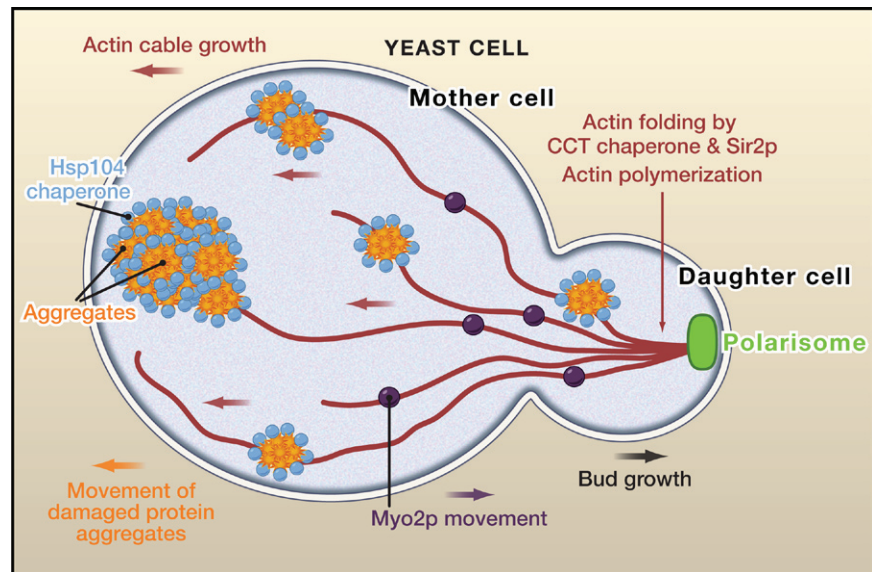


Figure 1. Keeping Daughters Youthful

Depicted is the retrograde flow of damaged protein aggregates along actin cables from the daughter bud to the mother cell during budding in yeast. CCT and Sir2p fold actin to provide the substrate for cable formation. Myo2p transports material into the bud for growth. Hsp104 binds to damaged protein aggregates to ensure their retrograde transport out of buds along actin cables.

to the damaged protein aggregates for retrograde transport is an interesting, unsolved problem.

As an antiaging gene, it is not surprising that *SIR2* protects daughter cells from aging-induced damage. To wit, previous findings showed that *SIR2* also protected daughter cells from extrachromosomal rDNA circles (ERCs), a toxic product of genome instability in aging mother cells (Sinclair and Guarente, 1997). Like damaged proteins, ERCs are inherited asymmetrically by mothers, and daughters are ERC free. However, in this case, *SIR2* is protective because it represses the formation of ERCs by silencing the chromatin of the ribosomal DNA. The retrograde transport of damaged proteins from buds goes a step further in that it allows the reversal of damage in daughters. Interestingly, the gene *BUD6*, which encodes a component of the polarisome, also affects inheritance of ERCs (Shcheprova et al., 2008). The authors suggest that *bud6* mutants might not display a short life span like other polarisome mutants because of opposing effects on the segregation of damaged proteins and ERCs.

The close link shown by Liu et al. between *SIR2* and cell polarity may bespeak an ancient connection between

antiaging mechanisms and asymmetric cell division. By this reckoning, asymmetric cell division affords an opportunity for youthful cells to be produced in each generation. Retrograde transport of damaged proteins from the new to the old cell thus may have evolved to take advantage of asymmetric cell division. However, as *SIR2* also regulates the mating process by silencing extra copies of a and α mating type information, the *SIR2*-polarisome connection may also relate to another aspect of mating—the polarized growth of cells toward one another during cell cycle arrest by a and α factors.

One wonders whether quality control mechanisms mediated by retrograde transport might apply in organisms with bona fide germ cells. If so, it is possible that asymmetric cell division during gametogenesis or fertilization, e.g., the formation of polar bodies from oocytes, provides an opportunity to purge zygotes of the detritus of aging in each generation. As an entry point to this problem, it will be interesting to see whether the progeny of *sir2* mutants (i.e., the products of *sir2* mutant gametes) show accelerated aging or other defects in the nematode *Caenorhabditis elegans*, the fruit fly *Drosophila*, or mice. In the case of mammalian SIRT1, this study is not possible because mice lacking SIRT1 are not

viable, but conditional strategies to inactivate SIRT1 spatially or temporally may be applicable.

Weismann recognized that his concept of the germ line could explain how nature trumped aging, at least at the species level. The findings of Liu et al. provide a molecular framework for how this crucial process can occur, and could eventually lead to new strategies to slow aging in the soma. A weight of evidence already indicates that SIRT1 protects somatic cells against aging by deacetylating factors regulating metabolic pathways, stress tolerance, and genomic stability (Finkel et al., 2009). This effect is enhanced when precious resources are shifted from germ line maintenance to somatic cell maintenance during food scarcity

(Kirkwood, 1977). Under these conditions, the premium may be on delaying reproduction until food becomes more available. The study by Liu et al. raises the fascinating possibility that SIRT1 is also called into action to promote germ cell quality control when resources are plentiful, that is, during times of food abundance.

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REFERENCES

- Aguilaniu, H., Gustafsson, L., Rigoulet, M., and Nyström, T. (2003). *Science* 299, 1751–1753.
- Erjavec, N., Larsson, L., Grantham, J., and Nyström, T. (2007). *Genes Dev.* 21, 2410–2421.
- Finkel, T., Deng, C.X., and Mostoslavsky, R. (2009). *Nature* 460, 587–591.
- Kirkwood, T.B. (1977). *Nature* 270, 301–304.
- Liu, B., Larsson, L., Caballero, A., Hao, X., Öling, D., Grantham, J., and Nyström, T. (2010). *Cell*, this issue.
- Moseley, J.B., and Goode, B.L. (2006). *Microbiol. Mol. Biol. Rev.* 70, 605–645.
- Shcheprova, Z., Baldi, S., Frei, S.B., Gonnet, G., and Barral, Y. (2008). *Nature* 454, 728–734.
- Sinclair, D.A., and Guarente, L. (1997). *Cell* 91, 1033–1042.
- Tong, A.H., Lesage, G., Bader, G.D., Ding, H., Xu, H., Xin, X., Young, J., Berriz, G.F., Brost, R.L., Chang, M., et al. (2004). *Science* 303, 808–813.
- Weisman, A. (1892). *The Germ Plasm: A Theory of Heredity* (New York: Charles Scribner's Sons).

Duct Tape for Broken Chromosomes

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A cell undergoing mitosis is presented with a potentially catastrophic situation when a DNA double-strand break creates a chromosome fragment that lacks connection to a centromere. Royou et al. (2010) now reveal that this cellular crisis is averted in fruit fly neuroblasts by thin chromatin tethers that hold on to the ends of the broken chromosomes.

How does a cell in mitosis cope with a broken chromosome? According to findings presented by Royou et al. (2010) in this issue, neuroblasts in the fruit fly *Drosophila* have the capacity to reattach the broken pieces with thin tethers that contain DNA and some familiar mitotic proteins. Remarkably, in many cases, this emergency fix lasts long enough to allow the completion of cell division and can even rescue larval development.

In mitosis two sister kinetochores are built at the centromeres of each chromosome. The kinetochores attach to the mitotic spindle microtubules and move the chromosomes to align them at the metaphase plate. Then, at anaphase each chromosome separates into two chromatids that are ferried to opposite

poles by kinetochores. Given the prominence of kinetochores in chromosome segregation, conventional wisdom suggests that chromosome fragments lacking centromeres would fail to segregate properly during mitosis. However, some studies report that the segregation of chromosome fragments lacking centromeres is remarkably resilient over several cell divisions (Malkova et al., 1996; Titen and Golic, 2008).

To create acentric chromosome fragments under controlled conditions, Royou et al. expressed I-Crel endonuclease under the control of a heat shock promoter in third instar larvae. I-Crel induces a double-strand break at an endogenous 20 nucleotide sequence within the ribosomal DNA located on

Drosophila sex chromosomes. As a consequence, I-Crel expression causes the *Drosophila* X chromosome to break into two pieces, a small fragment containing the centromere and a long acentric chromosome arm. Remarkably, the acentric fragments segregate successfully through multiple rounds of cell division, and their induction causes no detectable impairment in the development of third instar larvae into adult flies (though I-Crel expression does cause significant lethality when induced at earlier stages).

The authors examined larval neuroblasts expressing I-Crel by cytology and fluorescence video microscopy and find that they exhibit normal chromosomal alignment at metaphase. However, at anaphase there are a few lagging chro-