Nature Reviews Molecular Cell Biology | AOP, published online 6 August 2008; doi:10.1038/nrm2470

AGEING

Turning back the clock

> “…[a] diffusion barrier in the nuclear envelope controls the retention of ageing determinants in mother cells…”

How many times have you looked at the mirror wondering: “I wish I could turn back the clock”? Unfortunately, the ageing clock is only set once, at birth. However, Yves Barral and co-workers now provide insights into the molecular mechanism that can reset the ageing clock, at least in yeast.

Budding yeast cells divide asymmetrically through budding of the daughter cell from the surface of its mother. Mother cells age over generations, whereas the daughter cells (buds) are born young and their lifespan remains constant irrespectively of the age of their mother when they are born.

To identify the mechanism that protects daughter cells from ageing, the team used green fluorescent protein (GFP)-tagged reporters and fluorescence loss in photobleaching to monitor the dynamics of different nuclear compartments during anaphase. They observed that nuclear pore complexes (NPCs) moved freely throughout the nuclear envelope but once the nucleus penetrated into the bud, a diffusion barrier prevented the pre-existing (old) NPCs from moving to the daughter cell through the bud neck, whereas NPCs in the buds were inserted *de novo*.

Because the diffusion barrier always co-localizes with the bud neck, the authors tested whether bud-neck proteins are important for the formation and maintenance of the diffusion barrier. They found that a large fraction of old NPCs moves to the bud in yeast strains lacking septins or in mutants for the bud-neck protein Bud6 (*bud6*Δ).

The accumulation of extrachromosomal ribosomal DNA circles (ERCs) in mother nuclei contributes to yeast ageing. To address whether the diffusion barrier is responsible for protecting the daughter cell from ERC accumulation, the authors monitored the distribution of a tagged plasmid that behaves like ERC by time-lapse microscopy in wild-type and *bud6*Δ strains. They showed that the retention of plasmids in mother cells depends on the diffusion barrier. Furthermore, the plasmids are tightly associated with NPCs and can accumulate in the buds in nuclear pore mutant strains, even in the presence of the diffusion barrier. Therefore, the accumulation of ERC plasmids in mother cells depends on their anchorage to NPCs and on the Bud6- and septin-dependent diffusion barrier, which keeps these NPCs and the associated plasmids to the mother side of the nucleus.

Finally, to test whether the disruption of the diffusion barrier affected bud rejuvenation, the team monitored the longevity of wild-type and *bud6*Δ cells and that of the buds that derived from them. Mutant cells failed to reset the age of their buds, which are the same age as their mothers.

This study demonstrates that a Bud6- and septin-dependent diffusion barrier in the nuclear envelope controls the retention of ageing determinants in mother cells during asymmetric cell division. So, yeast cells at least can reset the ageing clock.

Francesca Cesari

ORIGINAL RESEARCH PAPER Shcheprova, Z. *et al.* A mechanism for asymmetric segregation of age during yeast budding. *Nature* 27 July 2008 (doi:10.1038/nature07212)