electrochemical measurements to monitor changes in the electronic properties of the diamond surface when single-stranded DNA molecules, complementary in structure to that of the tethered DNA, were trapped from solution by the nanowire-supported DNA. Their results showed that trapping complementary DNA interferes with electron-transfer processes in the nanowires, thereby providing an electrical read-out. The resulting sensor could detect exceptionally low levels of the DNA analyte.

So how is the electrical signal in Yang and colleagues' method generated? Several mechanisms could apply. Diamond is a semiconductor, which means that its electrical properties can be altered by externally applied electric fields. DNA molecules are negatively charged, and so, when bound close to a diamond surface, they can induce an electric field that alters the conductivity of the diamond in what is known as a field effect. Another possibility depends on the conductivity of DNA itself. Hybridization of single-stranded DNA into the double-stranded form leads to an increase in the conductivity of the molecules, an effect that is generally attributed to the closer proximity of the electron systems of the DNA bases in the duplex[12].

Yang *et al.*[1] used several electrochemical measurements to try to understand the physical origin of the electrical signals, with conflicting results. Their cyclic voltammetry experiments (which measured the current through their sensor in response to voltage) showed that DNA hybridization decreased the conductivity of the nanowires, whereas impedance measurements (which characterized the electrical response of the system at specific frequencies of alternating current) suggested the reverse effect. The reason for this discrepancy is unknown, but will probably be a consequence of the electron-transfer and diffusion processes that occur at the surfaces of complex nanostructured materials. More work is clearly needed to understand this. Unravelling the origins of the electrical signals will also be crucial to developing robust analytical devices in the future.

Ultimately, the sensitivity of biosensors that rely on surface-derivatized components is limited by the physical parameters that govern the adsorption of DNA to those surfaces[13]. Similar limits of detection to that of Yang and colleagues' biosensor[1] have been achieved by diamond-based field-effect transistors[6], suggesting that there may be several approaches to converting biological signals into electrical ones that take advantage of diamond's extraordinary properties. Nevertheless, the authors' discovery might trigger the development of sensors for clinical diagnostics, environmental sensing and other applications at the interface between biology and microelectronics. ■

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CELL BIOLOGY

A molecular age barrier

Matt Kaeberlein

A mother's instinct is to protect her children at any cost. In the budding yeast *Saccharomyces cerevisiae* this 'maternal instinct' comes at a high price — accelerated ageing and premature death.

Cells of budding yeast divide asymmetrically, with the larger mother cell easily distinguishable from her daughter. This asymmetry, which is not just structural but also affects the distribution of cellular components, ensures a type of ageing in yeast — replicative ageing — that is defined by the number of daughter cells a mother produces[1]. Some years ago, a diffusible senescence factor associated with replicative ageing was discovered[2,3]. Over most of the course of the mother cell's lifespan, this factor is successfully retained in the mother, allowing each daughter cell to begin life relatively free of age-associated damage. In very old mother cells, however, the 'age barrier' becomes overburdened, leading to loss of asymmetry and premature daughter-cell senescence. On page 728 of this issue, Shcheprova *et al.*[4] provide insight into a nuclear age barrier in yeast, and show that, surprisingly, it limits longevity in both mother and daughter cells.

Several types of molecular damage are

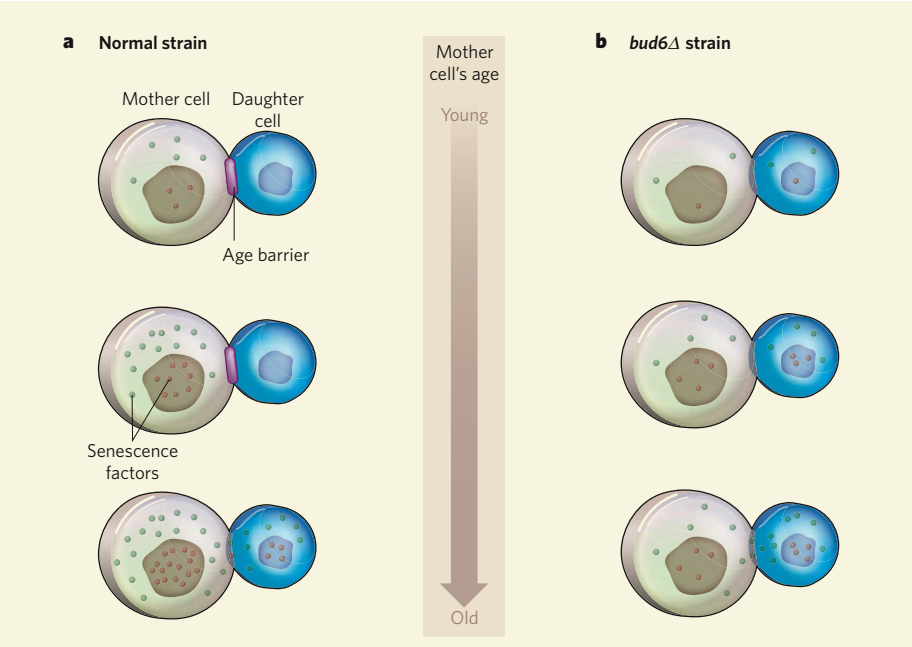

Figure 1 | Shared ageing. During cell division, normal young yeast mother cells asymmetrically retain a diffusible senescence factor. This factor may be a composite of damage-inducing nuclear factors, including extrachromosomal ribosomal-DNA circles (ERCs), and cytoplasmic components such as oxidatively damaged proteins and dysfunctional mitochondria. On the basis of Shcheprova and colleagues' identification[4] of a nuclear age barrier in yeast, which limits the passage of ERCs from mother cell to daughter cell, a general model can be proposed. **a,** During replicative ageing of normal yeast cells, an age barrier prevents the passage of various senescence factors to daughter cells. But if the mother cell replicates very late in life, this barrier breaks down. **b,** In a mutant that lacks the age barrier (such as *bud6*Δ), population lifespan could be increased owing to equal distribution — and so decreased accumulation — of damage to both mother and daughter cells.

thought to contribute to ageing in yeast. The best studied of these are extrachromosomal ribosomal-DNA circles (ERCs) — self-replicating plasmids formed by the process of homologous recombination within ribosomal DNA[5]. Consistent with their role as a senescence factor, ERCs are preferentially retained in the mother-cell nucleus and accumulate with age[5]. Mutations that accelerate the rate of ERC formation shorten replicative lifespan, whereas those that reduce ERC accumulation enhance longevity.

Besides ERCs, dysfunctional mitochondria and proteins damaged by reactive oxygen species are actively retained by mother cells and have also been implicated in replicative ageing[6–8]. Although the importance of such cytoplasmic factors in yeast ageing is less established than that of ERCs, it seems that the accumulation of damage in several mother-cell compartments results in replicative ageing.

Shcheprova *et al.*[4] advance our understanding of asymmetry between yeast mother and daughter cells, and its importance in ageing, by identifying a diffusion barrier that compartmentalizes the nuclear envelope during budding. This barrier's formation depends on septin proteins, which assemble into a ring around the bud neck and prevent the passage of pre-existing nuclear pores to the daughter cell. Circular DNA molecules (such as ERCs) — and presumably other asymmetrically inherited nuclear factors — are associated with these nuclear-pore complexes, and so are also unable to cross the barrier. This partitioning process requires Bud6, a protein that localizes to the bud neck. Yeast mother cells — and daughter cells — in which the gene encoding this protein has been deleted (*bud6*Δ cells) no longer retain pre-existing nuclear-pore complexes and ERCs, and are consequently long-lived (Fig. 1). This indicates that the presence of the nuclear age barrier limits longevity.

The authors' observations raise some perplexing and intriguing questions. For example, it is not clear why loss of ERCs' asymmetrical distribution increases replicative lifespan. If *bud6*Δ daughter cells inherit ERCs at birth, it seems counterintuitive that they should be long-lived. This apparent paradox can be explained if the ability of an ageing mother cell to pass ERCs to daughter cells more than compensates for the ERCs she herself inherited at birth (Fig. 1). Accordingly, although the daughter cells that arise from young *bud6*Δ mother cells (those that have been through fewer than about eight replicative cycles) inherit some damage at birth, they also go on to continually transfer damage to each of their own daughter cells and, consequently, live longer than do normal cells. Because ERCs and possibly other ageing factors accumulate with age, daughter cells arising from aged *bud6*Δ mother cells (those that have been through more than eight replicative cycles) will inherit a damage burden sufficient to shorten their lifespan. But as the proportion of mother cells of this age or older in the overall *bud6*Δ yeast population is small, the proportion of daughters derived from aged cells is also small. As a result, the average lifespan of the population is increased.

The longer lifespan of *bud6*Δ cells indicates that promoting longevity is not the primary function of the nuclear age barrier. Instead, it may be that, although the barrier ultimately limits population lifespan, it also confers a selective advantage — which is not directly related to ageing — on the daughter cells during the first few cell divisions, when natural selection is strongest. This may occur, for example, by allowing damage-free daughter cells to divide more rapidly or to respond to environmental changes more efficiently. Moreover, it may be that the barrier also functions to modulate asymmetrical inheritance of non-nuclear components. In this regard, it is noteworthy that the same team[4] has previously described[9] a similar Bud6- and septin-dependent barrier that limits diffusion of proteins in the endoplasmic reticulum across the bud neck. Whether *bud6*Δ cells are also defective for asymmetrical inheritance of cytoplasmic components remains unknown, and must be explored.

Can Shcheprova and colleagues' observations[4] inform us about aspects of human ageing — aside from the occasional certainty that our kids are, indeed, making us old before our time? Obvious counterparts of Bud6 and the septin ring do not seem to exist in mammals, and there is no evidence that ERCs contribute to ageing in multicellular organisms. Nonetheless, several genetic factors that modulate replicative ageing in yeast have a similar role in determining lifespan in the nematode worm *Caenorhabditis elegans*[10]. From an evolutionary point of view, yeast and worms are more distantly related than worms and humans, so it is reasonable to speculate that some of these conserved longevity genes also modulate ageing in humans. Moreover, one can imagine that asymmetrical inheritance of damage is likely to occur in certain types of human cell, and that it could be associated with age-related cellular dysfunction and disease. So, as our knowledge of the molecular nature of replicative asymmetry in yeast grows, it is crucial to extend these findings, where possible, to multicellular model systems. Such studies may provide insight into the molecular processes that contribute to ageing and facilitate the development of therapies for various age-related diseases. ■

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PALAEONTOLOGY

Bite size

S. STAMMERS/SPL

Ten thousand or so years ago, the lineage of sabre-toothed cats came to an end. Per Christiansen has revisited the evolutionary history of this distinctive group and that of the other members (felines) of the cat family, with particular reference to changes in the shape of their skull and mandible. He describes his work, which bears on the lively issue of the cause of the sabretooths' demise, in *PLoS ONE* (P. Christiansen *PLoS ONE* **3,** e2807; 2008). It scarcely needs pointing out that the characteristic feature of these cats was their enlarged upper canines, as seen here in this skull of *Smilodon*.

Christiansen's sample encompassed 24 feline species and 9 fossil sabretooths. He aimed for a comprehensive analysis of differences in the cranio-mandibular morphology of these specimens by including data on 39 features, so as to offer an evolutionary account that is normalized for body size and set in overall 'morphospace'.

He concludes that the early sabre-toothed cats were not fundamentally distinct from felines, but that different selective pressures came into play as the later (derived) sabretooths evolved. These species set off on an evolutionary trajectory that set a premium on precision killing with large canines. This involved maximizing the extent of their gape, and so a radical reshaping of their skull and mandible. But it came at the expense of a reduction in bite force.

Such specializations depended on the availability of large prey, and required the predator to be large. By contrast, the superior bite force of the cone-toothed felines allowed a greater variation in their size, as seen in the extant species, and a greater variation in prey size.

These new data, then, add to evidence that — as Christiansen puts it — the derived sabre-toothed cats found themselves in an ecological cul-de-sac as ecosystems and climate zones changed.

Tim Lincoln