peaking at more than 20–30 metres of slip off northern Sumatra (see Fig. 1 on page 47), the source region for the devastating Aceh tsunami. In the models, slip extends into the northernmost of the Andaman Islands, as surface deformation was observed as far north as Preparis Island, Myanmar. The analysis also shows that the giant earthquake (magnitude 9.1–9.2) was followed by weeks of slower deformation that accompanied thousands of aftershocks (Fig. 1). The results show that we have much to learn about how deformation is accommodated across these zones of dramatic plate convergence.

One of the most interesting aspects of the new geodetic models is the large amount of post-seismic slip, estimated at approximately 30% of that in the initial mainshock and corresponding to slip magnitudes comparable to those produced by an earthquake of magnitude 8.7. The substantial afterslip is similar to that seen with the 1960 magnitude-9.5 Chile earthquake sequence[7,8]. But unlike the afterslip in 1960, which is thought to have occurred at greater depth than the seismic rupture, the 2004–05 afterslip seems to have been located in the shallower regions of the plate boundary, adjacent to the seismic slip that occurred abruptly on the morning of 26 December.

The emerging picture is that of a frictionally heterogeneous plate boundary that contains large regions prone to slip during earthquakes and regions that slip more slowly, although both participate in megathrust earthquake sequences. Earthquake scientists have known for some time that mapping the regions prone to sudden slip and understanding how they evolve is essential for estimating the hazards posed by a particular fault. Understanding the correlations between the regions of large seismic slip and variations in upper-plate morphology and strength[9–11] may help to illuminate the frictional condition of the plate interface at depth. As work to integrate the available data continues, and new data on the Sumatra–Andaman plate-boundary structure are collected, perhaps we can test some of these ideas.

Many issues require deeper investigation. On 28 March 2005, a large rupture (Fig. 1) continued the sequence begun in December southeast along the Sunda arc. But why did this rupture occur 90 days after the mainshock? Subarya *et al.*[4] identify a particular fault in the Indian Ocean floor that possibly inhibited continuation of the initial rupture in that direction. But what process changed the situation during those 90 days — afterslip-induced fault loading, migrating fluids, an expanding deformation front, or something more complicated? And what caused the rupture to terminate in the north? Did it simply run out of strain energy as a consequence of plate-motion geometry? Or was something more complicated involved — perhaps related to the subduction of a large load of sediments from the Bay of Bengal, or an undiscovered feature of plate interactions in the region? What tectonic processes are operating in the region between this subduction zone and the Himalayan plate boundary that looms so close to billions of people?

Finally, will the sequence continue farther south? The occurrence of large earthquakes in the eighteenth and nineteenth centuries shows that large ruptures can hit this region, which includes southern Sumatra and Java (and so coastal populations of millions of people). If activity does migrate southwards, we will be better prepared with more adequate continuous GPS and seismic measurements, a result of international efforts. And at least one network is openly sharing data as they are recorded[12], which is necessary for timely and innovative integrations of the data. Perhaps these data will help in understanding the nature and implications of episodic tremor and slip before the next large subduction-zone earthquake occurs. ■

Charles J. Ammon is in the Department of Geosciences, Penn State University, 440 Deike Building, University Park, Pennsylvania 16802, USA.
e-mail: cammon@geosc.psu.edu

1. Rogers, G. & Dragert, H. *Science* **300,** 1942–1943 (2003).
2. Dragert, H., Wang, K. & James, T. S. *Science* **292,** 1525–1528 (2001).
3. www.usaid.gov/locations/asia_near_east/tsunami/trm.html
4. Subarya, C. *et al. Nature* **440,** 46–51 (2006).
5. Ammon, C. J. *et al. Science* **308,** 1133–1139 (2005).
6. Vigny, C. *et al. Nature* **436,** 201–206 (2005).
7. Linde, A. T. & Silver, P. *Geophys. Res. Lett.* **16,** 1305–1308 (1989).
8. Barrientos, S. E. & Ward, S. N. *Geophys. J. Int.* **103,** 589–598 (1990).
9. Wells, R. E., Blakely, R. J., Sugiyama, Y., Scholl, D. W. & Dinterman, P. A. *J. Geophys. Res.* **108,** 2507 (2003).
10. Song, T.-R. A. & Simons, M. *Science* **301,** 630–633 (2003).
11. Fuller, C. W., Willett, S. D. & Brandon, M. T. *Geology* **34,** 65–68 (2006).
12. www.tectonics.caltech.edu/sumatra/sugar.html
13. http://earthquake.usgs.gov/regional/neic

CELL BIOLOGY

Ageing nucleus gets out of shape

Hannes Lans and Jan H. J. Hoeijmakers

In certain premature-ageing syndromes, the architecture of the cell nucleus is abnormal. An animal model shows similar malformations during normal ageing, corroborating the idea that genome instability underlies ageing.

Hutchinson–Gilford progeria syndrome (HGPS) produces signs of dramatically accelerated ageing, such as early cessation of growth, baldness at the age of two, progressive degeneration of the skin, muscle and bone, and often fatal atherosclerosis (arterial plaque build-up) in childhood. Like many other premature-ageing syndromes, HGPS does not recapitulate all aspects of ageing — for example, patients show no neurodegeneration or cancer predisposition. HGPS and several other degenerative disorders are linked to defects in proteins that maintain the shape and organization of the nucleus, hinting that deteriorations in nuclear architecture may underlie some features of ageing. This notion is borne out by Haithcock *et al.*[1], who report in *Proceedings of the National Academy of Sciences* that progressive malformation of nuclei occurs with age in a classic animal model of ageing.

HGPS is associated with mutations in the nuclear protein lamin A (refs 2, 3). Lamin proteins polymerize to form an intranuclear scaffold known as the lamina, particularly around the edge of the nucleus. This lamina supports the nuclear architecture and helps to organize nuclear processes such as DNA and RNA synthesis[4,5]. A remarkable diversity of degenerative human disorders is linked to different mutations in lamin A: so far, 11 so-called laminopathies are known, several of which involve premature ageing (Table 1). The common HGPS mutation results in a deletion of 50 amino acids from the protein, and gradual accumulation of the truncated, abnormal lamin A probably affects lamina function. The cells of HGPS patients show progressive abnormalities in nuclear shape, including a folded nuclear envelope and loss of peripheral heterochromatin — the densely packed DNA that is normally found in a dim rim underlying the nuclear lamina[3,6]. This link between mutated lamin A and premature ageing does not, however, prove a causal role for nuclear architecture in normal ageing. In fact, the relevance of premature-ageing syndromes to normal ageing is highly controversial[7].

To find out whether changes in nuclear shape are associated with normal ageing, Haithcock *et al.*[1] turned to an animal model often used in ageing research: *Caenorhabditis elegans*, a nematode worm that is well known for its extreme-longevity mutants. The mean lifespan of this nematode is only two to three weeks, but it can be extended more than five times by downregulating the insulin/IGF-1 signalling pathway. This pathway controls metabolism and influences ageing rate in all organisms investigated, including mammals[8]. To visualize the nuclear lamina, the authors engineered a worm in which the single gene for lamin was fused to a gene encoding green fluorescent protein. The fluorescent lamin protein revealed age-related, progressive changes in nuclear lamina morphology in all cells except neurons and gametes. Whereas in young

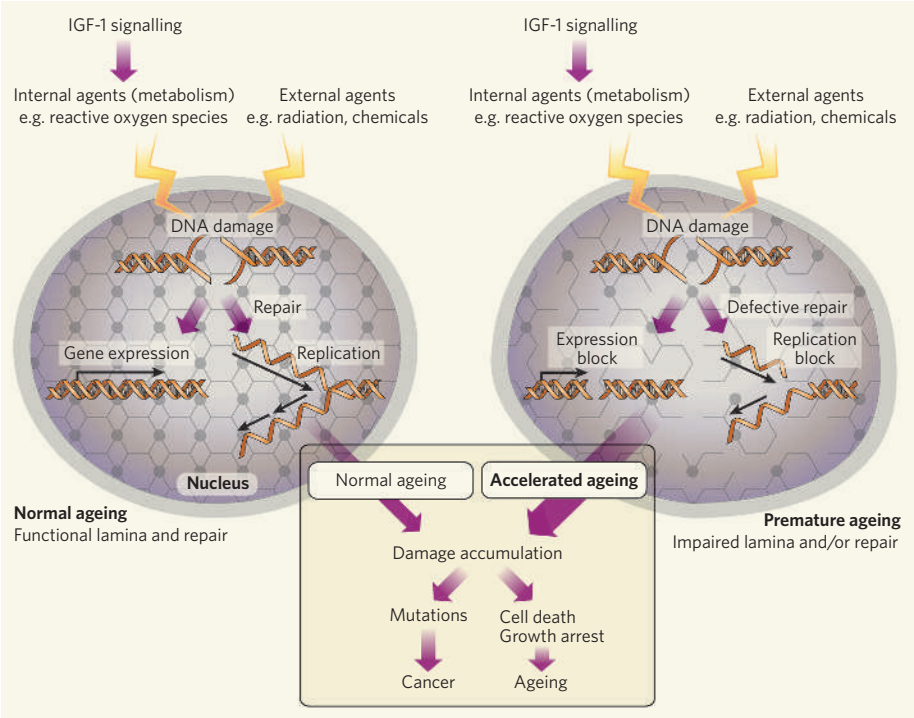

Figure 1 | Model linking normal and premature ageing with nuclear integrity and genome stability. Internal and external agents continuously damage DNA, creating a variety of harmful lesions. During normal ageing, most damage is efficiently repaired by various DNA-repair pathways, several of which are connected with gene expression and replication. Occasionally, damage leads to mutation, cell death or growth arrest, eventually causing cancer or ageing (depending on the type of damage and the pathways or cell types affected). In most premature-ageing syndromes (Table 1), DNA lesions cannot be efficiently repaired because of dysfunctional pathways for repair or damage signalling, or because the nuclear lamina is abnormal. The nuclear lamina indirectly affects genome stability because transcription and replication, and consequently also repair, take place in association with the lamina. Inefficient repair allows rapid accumulation of DNA damage, accelerating the onset of cancer or ageing.

animals the lamin protein was properly distributed around the nuclear periphery, with ageing its distribution became progressively irregular. Concomitantly, the nuclear shape changed and peripheral heterochromatin disappeared. Variations between animals and among cells underscored the stochastic nature of the changes.

Notably, the kinetics of the nuclear alterations seemed to be under the control of the insulin/IGF-1-like signalling system: the onset of severe nuclear morphological change was delayed in two long-lived *C. elegans* mutants, and it was correspondingly advanced in two short-lived animals. So, the nuclear changes seem to be connected with the normal ageing process. Although still correlative, these intriguing findings are highly reminiscent of progressive nuclear alterations found in cells of rapidly ageing HGPS patients[6] and in cells of naturally aged mammals[9]. This supports the parallel between ageing — whether normal, accelerated or delayed — and malformation of nuclei.

How can the accumulation of abnormal lamin A contribute to ageing? There are several hypotheses[4,5]. Structurally, lamin A dysfunction might make the nucleus more vulnerable to mechanical stress. Although appealing, this cannot be the only explanation because not all tissues affected in HGPS patients are subject to abnormal levels of mechanical stress (for example, fat tissue). Alternatively, lamin A interacts with a diverse array of gene regulatory factors, including pRB, which controls entry into the cell-division cycle and the balance between cell division and specialization. Accumulation of truncated lamin A may mean that its binding partners end up in the wrong place and disrupt their regulatory function, thereby promoting permanent growth arrest (senescence).

We would like to propose another option. Lamin A indirectly influences genome stability because the nuclear lamina is involved in processes such as replication and gene expression[10], and these processes are intimately linked with the signalling that follows DNA damage and DNA repair. Consequently, replication-associated repair (such as homologous recombination and mismatch repair), damage-tolerance mechanisms (such as translesion synthesis) and DNA-damage signalling may be compromised when the nuclear lamina is dysfunctional. Similarly, the transcription of genes is linked with the lamina and transcription-coupled repair is associated with the nuclear matrix[11]. This repair pathway promotes cell survival by allowing recovery of gene expression blocked by damage in the DNA template.

DNA damage inevitably occurs with time; for example, because oxidative respiration continually generates highly reactive oxygen species. So, the following sequence of events may be envisaged (Fig. 1). Disruption of the nuclear lamina compromises several DNA repair pathways. This triggers cell death and senescence upon damage induction, thereby promoting ageing. In support of this idea, there are signs of genome instability in HGPS cells and mouse mutants[12]. Additionally, mice with abnormal lamin A exhibit spontaneous activation of p53 protein, the guardian of genome integrity[13]. This would add the progeroid laminopathies to the growing list of other progeroid syndromes — which lead to accelerated ageing — that are all linked with impaired genome stability (Table 1).

This scenario may explain the connection between lifespan extension and insulin/IGF-1 signalling and caloric restriction, because oxidative metabolism is a substantial cause of DNA damage: the lower or more efficient oxidative respiration is, the fewer harmful reactive oxygen species are produced, and the longer the lifespan is. This could account for

Table 1 Progeroid syndromes associated with impaired genome stability*

Syndrome (affected genes)	Affected process
Cockayne syndrome (*CSA, CSB*)	Transcription-coupled DNA repair
Cerebro-oculo-facio-skeletal syndrome (*CSB, XPG, XPD*)	Transcription-coupled and global genome nucleotide excision repair
Trichothiodystrophy (*XPB, XPD, TTDA*)	Transcription-coupled and global genome nucleotide excision repair
Xeroderma pigmentosum + Cockayne syndrome (*XPB, XPF, XPD, XPG*)	Transcription-coupled and global genome nucleotide excision repair
Xeroderma pigmentosum + DeSanctis–Cacchione syndrome (*XPA, XPC, XPD*)	Global genome nucleotide excision and transcription-coupled repair
Ataxia telangiectasia (*ATM*)	DNA damage response
Nijmegen breakage syndrome (*NBS1*)	DNA damage response and repair
Bloom syndrome (*BLM*)	DNA repair and recombination
Werner syndrome (*WRN*)	DNA repair and recombination
Fanconi anaemia (*FANC* genes, *BRCA2*)	DNA crosslink repair
Dyskeratosis congenita (*DKC1, TERC1*)	Telomere maintenance
Hutchinson–Gilford progeria syndrome (*LMNA*)	Lamina function
Atypical Werner syndrome (*LMNA*)	Lamina function
Restrictive dermopathy (*LMNA, ZMPSTE24*)	Lamina function
Seip syndrome (*LMNA*)	Lamina function

*Mitochondrial DNA disorders that lead to premature ageing might also be considered to be caused by genetic instability.

why screens for mutants that have extended lifespans have never yielded genes associated with DNA repair. Apart from the fact that improving repair by single mutations is difficult, it would be impossible to improve many distinct repair systems simultaneously. Only numerous small evolutionary steps over long periods of time would eventually result in longer lifespan. However, the rate of metabolism is under the control of the single IGF-1 pathway, explaining why single mutants that reduce or enhance the rate of metabolism in general can retard or accelerate ageing, respectively, by regulating the cause of DNA damage.

Because genome stability *in toto*, including nuclear lamina function, covers almost all ageing features displayed in the wide spectrum of progeroid disorders, it is currently the most consistent parameter to underlie ageing. Thus, accelerated-ageing syndromes may be as significant for insight into normal ageing as cancer predisposition conditions have been for understanding cancer. Similarly, DNA damage may be as relevant for ageing as it is now recognized to be for cancer. ■

Hannes Lans and Jan H. J. Hoeijmakers are at the MGC-CBG Department of Cell Biology and Genetics, Erasmus Medical Center, PO Box 1738, 3000DR, Rotterdam, The Netherlands.
e-mail: J.Hoeijmakers@erasmusmc.nl

1. Haithcock, E. *et al. Proc. Natl Acad. Sci. USA* **102,** 16690–16695 (2005).
2. De Sandre-Giovannoli, A. *et al. Science* **300,** 2055 (2003).
3. Eriksson, M. *et al. Nature* **423,** 293–298 (2003).
4. Worman, H. J. & Courvalin, J. C. *Int. Rev. Cytol.* **246,** 231–279 (2005).
5. Smith, E. D. *et al. Mech. Ageing Dev.* **126,** 447–460 (2005).
6. Goldman, R. D. *et al. Proc. Natl Acad. Sci. USA* **101,** 8963–8968 (2004).
7. Miller, R. A. *Science* **310,** 441 (2005).
8. Kenyon, C. *Cell* **120,** 449–460 (2005).
9. Johnson, J. E. in *Ageing and Cell Structure* Vol. 2 (ed. Johnson, J. E.) 37–88 (Plenum, New York, 1984).
10. Stein, G. S. *et al. Trends Cell Biol.* **13,** 584–592 (2003).
11. Kamiuchi, S. *et al. Proc. Natl Acad. Sci. USA* **99,** 201–206 (2002).
12. Liu, B. *et al. Nature Med.* **11,** 780–785 (2005).
13. Varela, I. *et al. Nature* **437,** 564–568 (2005).

NANOTECHNOLOGY

How clean is too clean?

Ulrich Gösele

Silicon nanowires could form the building-blocks of future electronic devices, but under ultra-clean conditions, regulating their growth is difficult. Is the strictly controlled environment the problem?

At the heart of the success of microelectronic gadgets, from laptop computers to mobile phones and iPods, is the fact that silicon-based electronic devices keep getting smaller. In the most advanced of such devices currently in production, the smallest features that regulate the flow of current are less than 100 nanometres in size. But if the trend to miniaturization of these features is to continue — say, to scales below 10 nanometres — a new basic unit for electronics, other than the conventional silicon wafer, is required. Several candidate materials exist: carbon nanotubes, molecular switches and nanoscale silicon wires are examples. In a paper published online today, Hannon *et al.*[1] report *in situ* observations under an electron microscope of the growth of silicon nanowires in ultra-clean conditions*. Their observations might cast doubt on the suitability of such nanowires for mass production. They might, on the other hand, simply be telling us that the particular experimental conditions under which these nanowires were made were just too clean.

But first, some background. The idea of using nanowires of conventional semiconductors such as silicon or gallium arsenide as building-blocks of nanoelectronic or nanophotonic devices was introduced into mainstream research at the end of the 1990s (see, for example, ref. 2). These silicon nanowires are generally grown by the vapour–liquid–solid (VLS) method. In this, a tiny liquid droplet of a metal, such as gold, absorbs silicon from a gaseous precursor, such as silane (SiH_4) or disilane (Si_2H_6), with such efficiency that the gold–silicon alloy droplet becomes supersaturated with silicon. This supersaturation causes a single, cylindrical silicon crystal — the nanowire — to nucleate, with the diameter of the nanowire being determined by the size of the initial gold droplet.

The droplet remains at the tip of the nanowire, which grows steadily outwards from it. If the nanowire lies on the surface of a silicon single-crystal wafer, growth occurs 'epitaxially', that is, with the same crystal orientation as the underlying silicon. The fundamentals of this technique for the growth of silicon and other semiconductors were understood more than 40 years ago[3,4] for creating objects with diameters larger than 100 nanometres. But it was not until 1992 that the first electronic device on the nanoscale, based on gallium arsenide semiconductor nanowires, came to fruition[5].

The droplets at the tips of semiconductor nanowires that grow in parallel have generally been considered to be independent. But Hannon *et al.*[1] show that, under the ultra-clean, high-vacuum conditions of their special electron microscope, larger droplets grow at the expense of smaller ones. These smaller droplets then shrink away, preventing any further nanowire growth from them. This effect, known as Ostwald ripening — sometimes jokingly referred to as the capitalistic principle — is named after Wilhelm Ostwald, 1909 chemistry Nobel laureate, who explained the effect as resulting from a decrease in total surface energy that occurs when atoms are transferred by diffusion processes from smaller to larger crystals[6]. (For a mathematical treatment of the effect, see refs 7, 8.)

Such an energy-minimizing diffusion transfer requires the efficient transport of atoms between neighbouring gold droplets. This cannot occur through gaseous diffusion above the silicon wafer because of the extremely low vapour pressure of gold; equally, the transport of gold atoms through the bulk of the silicon is also negligible. Hannon *et al.*[1] argue convincingly that the mode of transport is surface diffusion, which requires not only a high diffusivity of gold on the silicon surface, but also a high solubility of gold on the surface or in a thin surface layer (Fig. 1). This would fit

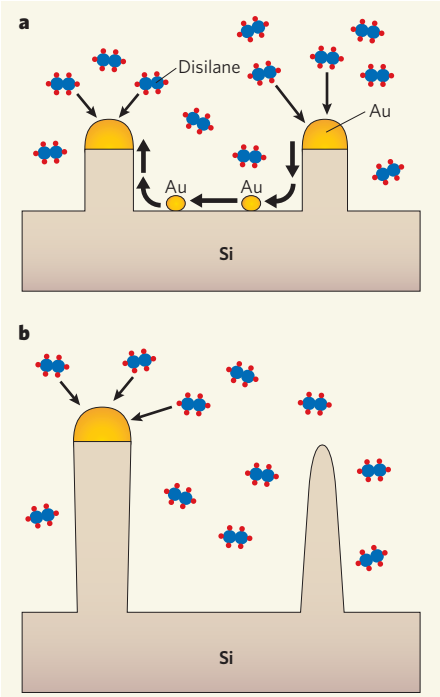

Figure 1 | Gold migration. A schematic cross-section of two silicon nanowires growing on a silicon substrate in a silicon-containing vapour (of silane, SiH_4, and disilane, Si_2H_6) by means of the vapour–liquid–solid (VLS) method, as used by Hannon *et al.*[1]. **a**, Two liquid-gold droplets are initially of slightly different size, causing a net diffusion flux of gold atoms from the smaller to the larger gold droplet through the Ostwald ripening mechanism along the silicon surface. **b**, Later, the smaller gold droplet has shrunk away completely, and its silicon nanowire has stopped growing. The implications of this effect for the mass production of silicon nanowires are potentially immense. (Dimensions not to scale; diameter changes exaggerated.)

*This article and the paper[1] concerned were published online on 29 January 2006.