Booker *et al.*[1] explain the deep melting by invoking the ideas of Bercovici and Karato[11]. This new hypothesis suggests that a layer of melt exists just above the 410-km boundary as slowly upwelling mantle undergoes a change from water-rich wadsleyite to olivine, liberating water and inducing melting. In Booker and colleagues' models, the melt column seems to originate as much from the 410-km boundary as it does from the subducting slab, and so the suggestion of a link between the two is not surprising. The authors propose that the liberation of additional water from the slab induces further production of buoyant melt, a necessary condition if the melt is to rise as is seen.

This link to Bercovici and Karato's model is intriguing, but I'm not completely sold on it. Undoubtedly, the argument would be strengthened by better data on the structure across the 410-km boundary which, as the authors point out, is not the best-resolved feature of the model. Booker *et al.* suggest that the mantle to the west of (or beneath) the slab is dehydrated as a result of melt extraction at the East Pacific Rise, part of the mid-ocean ridge system in the Pacific Ocean. Although this might be true for the upper 60–80 km or so of oceanic plate from which melt and water have been extracted, other data suggest that there is plenty of remaining water that can increase electrical conductivity in the mantle below about 80 km depth[12]. This means that only the region adjacent to the subducting slab would be expected to be dry. If there is water around, we would expect a more or less uniform increase in conductivity at 410 km across the region. Although their models show a stepwise increase across the 410-km boundary, Booker *et al.* point out that the data are consistent with a flat 410-km transition throughout the region. Why is all this important? Well, it speaks to outstanding issues in terms of resolution of this critical part of the system.

Regardless of the details of the 410-km boundary, the authors' primary observation — an electrical conductor that must surely represent a subduction-related melt column rising from depth — is striking. And, as they point out, issues pertaining to the 410-km boundary and the link to the Bercovici–Karato hypothesis can be addressed with measurements made with a longer chain of MT stations. If the interaction with a melt layer at 410 km is the explanation, it should be seen in other subduction systems. It hasn't been seen elsewhere yet, but maybe we just need to look more carefully. ■

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1. Booker, J. R., Favetto, A. & Pomposiello, M. C. *Nature* **429,** 399–403 (2004).
2. Hirth, G. & Kohlstedt, D. L. *Earth Planet. Sci. Lett.* **144,** 93–108 (1996).
3. Roberts, J. J. & Tyburczy, J. A. *J. Geophys. Res.* **104,** 7055–7066 (1999).
4. Karato, S. *Nature* **347,** 272–273 (1990).
5. Xu, Y. *et al. Science* **280,** 1415–1418 (1998).
6. Wannamaker, P. E. *et al. J. Geophys. Res.* **94,** 14127–14144 (1989).
7. Echternacht, F. *et al. Phys. Earth Planet. Inter.* **102,** 69–87 (1997).
8. Kirby, S. *et al. AGU Geophys. Monogr.* **96,** 195–214 (1996).
9. Hacker, B. R. *et al. J. Geophys. Res.* **108,** doi:10.1029/2001JB001129 (2003).
10. Kay, S. M. & Gordillo, C. E. *Contrib. Mineral. Petrol.* **117,** 25–44 (1994).
11. Bercovici, D. & Karato, S. *Nature* **425,** 39–44 (2003).
12. Lizarralde, D. *et al. J. Geophys. Res.* **100,** 17837–17854 (1995).

Ageing

Mice and mitochondria

George M. Martin and Lawrence A. Loeb

It can be hard to work out whether particular events are a cause or a correlate of ageing — do mutations in mitochondrial DNA, for instance, speed up the process of growing old? Some clever studies suggest so.

Mitochondria are little pockets of energy within cells, shouldering the important task of converting food into usable energy forms. To meet demands, every cell contains thousands of them. Unlike most other cellular compartments, mitochondria have their own genomes, which encode a few mitochondrial proteins (most others being encoded by genes in the nucleus). In numerous non-reproductive tissues of many species, mitochondrial genes (like nuclear genes) accumulate mutations as the animals age[1], and it has been speculated that these mutations might in fact cause ageing, by leading to energy-generation defects — increased numbers of harmful reactive oxygen species, cellular damage and so on. On the other hand, the association between mitochondrial mutations and ageing could merely be correlative — these mutations might simply be one of the manifestations of growing old. That possibility becomes less likely, however, with the publication of the paper on page 417 of this issue by Trifunovic and colleagues[2].

Point mutations (single base-pair changes)[3], deletions and rearrangements[4] in mitochondrial DNA accumulate in several non-reproductive (somatic) tissues during ageing. To find out whether such alterations are a cause or a correlate of growing old, Trifunovic *et al.*[2] genetically engineered mice to carry mutations in an enzyme called DNA polymerase-γ. Encoded by nuclear genes and transported to mitochondria, this protein is believed to be responsible for all aspects of mitochondrial DNA metabolism: it both copies and proofreads the DNA, eliminating errors it makes during replication, and it is also believed to participate in the resynthesis of DNA during DNA-repair processes. New mitochondria replace old mitochondria in all cell types throughout life, and new mitochondria must also be made when cells divide. These events require the replication of mitochondrial DNA.

Trifunovic and colleagues wanted to render the mitochondrial DNA polymerase error-prone by eliminating its proofreading activity while maintaining its catalytic potency — the rationale being that any errors in mitochondrial DNA replication would go unnoticed by the cell, and so mutations would accumulate. As the mice would have this error-prone polymerase from youth, it would be possible to see whether or not the mutations it produces accelerate ageing. To eliminate the proofreading activity, the authors substituted an alanine amino acid for a crucial aspartate in the relevant region of the enzyme molecule.

They found that the somatic tissues of mice bearing two mutant copies of the DNA polymerase-γ gene indeed showed extensive mitochondrial DNA mutations, largely comprising deletions and point mutations. The percentage of mitochondria bearing deletions was similar in different tissues, and did not vary with age, suggesting that the deletions had occurred early in development.

Mutated protein	Effects
Lamin A/C (ref. 11)	Defective inner nuclear membrane
Ku86, XPD (refs 12, 13)	Defective metabolism of nuclear DNA
DNA polymerase-γ (ref. 2)	Defective metabolism of mitochondrial DNA
Telomerase (ref.14)	Defective regulation of chromosome caps
p53 (ref. 15)	Altered regulation of cell-division cycle and cell death
Klotho (ref. 16)	Impaired calcium and vitamin D metabolism?

Figure 1 **Many mutational pathways can accelerate 'segmental ageing' (or, to use more conservative nomenclature, segmental ageing-like syndromes[10]) in mice. Published literature[2,11–16] suggests that there may be at least six pathways that generate partially overlapping subsets of features consistent with accelerated ageing. Several of these pathways are likely to interact[17], making such classifications problematic. Trifunovic and colleagues' findings[2], however, provide strong direct support for the mitochondrial pathway.**

The deletions seemed to have converted the normally circular mitochondrial DNA into linear molecules, which might not be functional inside cells.

Point mutations were also common; one mitochondrial enzyme, for instance — cytochrome *b* — had a three- to fivefold increase in single-base substitutions, randomly dispersed throughout the gene. The mutant animals also showed a decrease in the activity of enzymes involved in the respiratory chain (a crucial series of events in respiration) and the production of ATP (the main cellular energy store), which could be a result of both the deletions and the point mutations. The mutant mitochondrial DNA molecules were present together with normal copies, but sometimes a particular mutation would come to dominate — a situation comparable to that seen in ageing humans[5].

Strikingly, the mutant mice showed symptoms consistent with accelerated ageing, such as premature weight loss, hair loss, reductions in fertility, curvature of the spine and a shortened lifespan. The symptoms began to emerge at about 25 weeks of age — young adulthood, in mouse terms. These findings strongly support the idea that mutations in mitochondrial DNA can cause at least some features resembling ageing. This delayed, post-maturational expression of overt signs of ageing is an important feature of any useful model system for studying the mechanisms by which organisms grow old.

Trifunovic and colleagues' findings are also consistent with the oxidative-damage theory of ageing — the idea that ageing is caused by an increase in the steady-state levels of reactive oxygen species and by proton 'leaks'. Such events can result from mutations in respiratory-chain proteins.

Interestingly, there is a human disease that might be considered as a parallel to these mutant mice. Like mouse DNA polymerase-γ, the human enzyme contains DNA-synthesizing and proofreading domains[6]. Mutations in the proofreading domain are among the genetic alterations responsible for a rare inherited human disease, progressive external ophthalmoplegia[7], which is characterized by paralysis of the eye muscles and various effects on other organs, and by the accumulation of mitochondrial mutations in non-reproductive tissues[8]. Like other mitochondrially linked, inherited disorders, the disease typically exhibits a delayed onset and a progressive course — features shared with ageing.

As with the mutant mice, however, many characteristics of interest to gerontologists have not been investigated in the rare affected people. More information is needed, in both mice and humans, about the ages of onset and rates of progression of cataracts, visual degeneration and hearing loss, and changes in immunity, hormones, cognitive functions and other traits.

Nonetheless, Trifunovic and colleagues' elegant study[2] establishes that several manifestations of ageing in mice can result from mutations in DNA polymerase-γ that induce error-prone mitochondrial DNA synthesis. These results do not, however, imply that this is the only pathway that generates abnormalities resembling ageing. There are several other DNA-replicating and proofreading polymerases (α, β and δ) that function in the nucleus, as well as at least eight newly discovered, naturally error-prone polymerases that are believed to function in bypassing nuclear DNA lesions or in specialized processes that affect DNA[9]. These nuclear enzymes might, when mutated, each lead to further genetic alterations in certain somatic tissues and so accelerate ageing. If experiments show this to be the case, these polymerases will join the growing list of proteins that, when mutated in mice, produce groups of features that hint at an acceleration of particular aspects of ageing ('segmental ageing'; Fig. 1); many of the mutations could act by enhancing genomic instability.

Of higher priority, however, would be experiments aimed at finding ways of maintaining the structure and function of tissues and organs for longer periods — leading to lengthened, not abbreviated, lifespans. We therefore look forward to the availability of mice that have been modified to bear a mitochondrial DNA polymerase that is more accurate than the normal enzyme. ■

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1. Vijg, J. *Mutat. Res.* **447,** 117–135 (2000).
2. Trifunovic, A. *et al. Nature* **429,** 417–423 (2004).
3. Wang, Y. *et al. Proc. Natl Acad. Sci. USA* **98,** 4022–4027 (2001).
4. Melov, S., Hinerfeld, D., Esposito, L. & Wallace, D. C. *Nucleic Acids Res.* **25,** 974–982 (1997).
5. Nekhaeva, E. *et al. Proc. Natl Acad. Sci. USA* **99,** 5521–5526 (2002).
6. Lim, S. E., Longley, M. J. & Copeland, W. C. *J. Biol. Chem.* **274,** 38197–38203 (1999).
7. Agostino, A. *et al. Neurology* **60,** 1354–1356 (2003).
8. Del Bo, R. *et al. Neurology* **61,** 903–908 (2003).
9. Shcherbakova, P. V., Bebenek, K. & Kunkel, T. A. *Science Sci. Aging Knowledge Environ.* doi:10.1126/sageke.2003.8.re3 (2003).
10. Martin, G. M. *Birth Defects Orig. Artic. Ser.* **14,** 5–39 (1978).
11. Mounkes, L. C., Kozlov, S., Hernandez, L., Sullivan, T. & Stewart, C. L. *Nature* **423,** 298–301 (2003).
12. Vogel, H., Lim, D. S., Karsenty, G., Finegold, M. & Hasty, P. *Proc. Natl Acad. Sci. USA* **96,** 10770–10775 (1999).
13. De Boer, J. *et al. Science* **296,** 1276–1279 (2002).
14. Rudolph, K. L. *et al. Cell* **96,** 701–712 (1999).
15. Tyner, S. D. *et al. Nature* **415,** 45–53 (2002).
16. Nabeshima, Y. *Ageing Res. Rev.* **1,** 627–638 (2002).
17. Orsini, F. *et al. J. Biol. Chem.* doi:10.1074/jbc.M401844200 (2004).

Geochemistry

Warm debate on early climate

Timothy W. Lyons

Would Earth's early ocean have been a frozen wasteland had levels of atmospheric methane not been sky high? Maybe. Or maybe, according to a new view of an old idea, the main warming agent was carbon dioxide.

For the first three-and-a-half billion years of Earth's history, the Sun burned only about 70–90% as brightly as it does today. A famous paradox of ancient climate demands that we reconcile the persistence of a life-sustaining liquid ocean with these less-warming rays from a faint young Sun. The solution lies with greenhouse gases[1], which trap heat near the planet's surface. In recent years, methane has become the favoured greenhouse agent, overcoming the earlier popularity of carbon dioxide in climate models spanning most of the Precambrian eon — that is, during all of Earth's history up to about three-quarters of a billion years ago, after which life emerged on a large scale.

On page 395 of this issue, Ohmoto and his colleagues[2] dispute the arguments against CO_2. Their challenge has additional significance because the assertion of inadequate CO_2 is the most frequently cited evidence for the existence of high levels of atmospheric methane. And given the incompatibility of methane and oxygen, this debate speaks more broadly to the oxygenation history of the atmosphere and its link to the evolution of early life.

Today, most of us worry about the 30% rise in levels of CO_2 since the Industrial Revolution and how that may drive global warming. But a generation of models of Earth's atmosphere invoked CO_2 concentrations as high as a thousand times greater than those of today to explain the unfrozen early ocean[1]. About a decade ago the idea of CO_2 as the dominant greenhouse agent was dealt a blow when Rye and his co-workers[3] used the absence of siderite, an iron-rich carbonate mineral, in ancient soils to set a maximum for CO_2 levels in the atmosphere 2.2 billion to 2.75 billion years ago (Fig. 1, overleaf). This maximum, although still many times the concentration observed today, was well below that necessary to offset the faint young Sun.

Rye *et al.* were compelled to suggest that another greenhouse gas — methane — must have taken up the slack. But their story was based on only a handful of data and assumed, among other things, that original mineral constituents and chemical properties