

Mito-communications

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(Received 19 January 2009; accepted 24 January 2009)

Age-related selection in mitochondrial genomes

The mitochondrial theory of ageing proposes that senescence is governed by the accumulation of deleterious mutations in somatic mitochondria. Partly because of this theory, there has been a great deal of interest in the idea that selection for increased longevity might have important consequences for the evolution of the mitochondrial genome (see, for example, Nabholz et al. 2008).

A recent study by Min and Hickey (2008) reports that mammals with longer generation times tend to have a significantly higher mitochondrial GC content than their faster-reproducing relatives. In combination with other studies that have shown a tendency for oxidative damage to promote GC to AT mutations, the authors interpret their result as evidence that the mitochondrial DNA of longer-lived species experiences less oxidative damage than that of their shorter-lived relatives. This reduction in DNA damage should, according to the mitochondrial theory of ageing, reduce the rate of senescence and lead to increased longevity.

But how do longer-lived species protect their mitochondrial DNA? Min and Hickey (2008) suggest that the amino-acid content of the mitochondrial proteins themselves might be the key. For instance, it has been shown that threonine metabolites can lead to increased levels of oxidative damage, and the authors present evidence that mitochondrial threonine has been selectively replaced in the human lineage since the human–chimpanzee divergence. It is suggested that this selective

removal of threonine was instrumental in the evolution of longer lifespans in the human lineage. This part of the story, however, is far from cut and dried—another recent study has shown that, for primates in general, longer-lived species tend to have higher levels of threonine in their mitochondrial proteins (Kitazoe et al. 2008).

Min and Hickey's (2008) study adds to a growing body of work that suggests there are strong links between mitochondrial protein structure, DNA damage, ageing, and mitochondrial genome evolution (Nabholz et al. 2008; Kitazoe et al. 2008; Bender et al. 2008; Moosmann and Behl 2008). The exact nature of many of these links, however, remains elusive.

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Mitochondrial evolution in tuatara

The tuatara (genus *Sphenodon*), endemic to New Zealand, is the sole relict of the reptilian order Sphenodontia. The species is characterized by a slow rate of morphological evolution, having shown little change over a period of at least 200 million years, leading to its reputation as a “living fossil”. Along with its long generation time, slow metabolism, and slow reproductive rate, this makes the tuatara a particularly interesting species from a biological perspective. In a report published in *Trends in Genetics*, Hay et al. (2008) presented a surprisingly high estimate of the mitochondrial substitution rate in tuatara (1.56 substitutions per site per million years). As the authors pointed out, this is nearly eight times higher than traditional, phylogeny-based estimates of the vertebrate substitution rate for the same section of the mitochondrial genome.

To obtain their rate estimate, the authors sequenced the mitochondrial hypervariable regions of 33 ancient and 41 modern tuatara samples. The ages of the samples, which were known either through radiocarbon dating or from the estimated ages of associated sampling layers, provided sufficient calibrating information to infer the evolutionary rate. The high estimated rate led Hay et al. (2008) to suggest a decoupling of molecular and morphological rates of evolution in the tuatara.

In a subsequent issue of the same journal, Miller et al. (2009) criticized the tuatara study, claiming that the high-rate estimate was the artefactual result of applying a parameter-rich method to an uninformative dataset. Even when the ages of the ancient tuatara samples were randomized, the method seemed to yield rate estimates resembling that originally obtained by Hay et al. (2008). Additionally, Miller et al. (2009) suggested that the tuatara sequences were not sampled from a panmictic population, thereby violating one of the assumptions of the method used to estimate the rate. By restricting their re-analysis to the ancient individuals, which were presumably drawn from a contiguous population, Miller et al. (2009) obtained a revised rate estimate of 0.076 substitutions per site per million years.

The authors of the original study have responded to these concerns (Subramanian et al. 2009). First, they indicate that the genetic diversity among the tuatara samples is comparable with that of previous ancient DNA data. They then repeat the date-randomization analysis of Miller et al. (2009), not just with the ancient samples but also including the modern samples. Subramanian et al. (2009) find that their original rate estimate could not be recovered under these conditions. Finally, they demonstrate that there is no apparent signal of phylogeographic structuring in tuatara mitochondrial DNA.

While Subramanian et al. (2009) have presented a well-reasoned defence of their original work, it appears that further analyses using a larger dataset will be

required to separate confidently the true evolutionary rate from potential estimation artefacts.

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Mitochondrial genome of the thylacine

In recent years, several Australian and international research programmes have targeted the thylacine (*Thylacinus cynocephalus*), popularly known as the Tasmanian tiger, a carnivorous marsupial that ranged throughout mainland Australia, Tasmania, and New Guinea. Since the last known individual died at Hobart Zoo in 1936, the thylacine has continued to draw interest from cryptozoologists and the general public, with hundreds of unconfirmed sightings. It is one of a handful of extinct organisms, along with the woolly mammoth, that have been earmarked for potential resurrection.

In an article published in *Genome Research*, Miller et al. (2009) report complete mitochondrial genome sequences from two thylacine individuals. Both sequences were generated from the hair shafts of museum specimens: one dried skin and one whole, ethanol-preserved organism. By using next-generation sequencing technology, the authors obtained mitogenomic sequences with 50–67-fold mean coverage. The sequence reads also included a large amount of contamination, from humans and microorganisms, as well as ~20 million base pairs of the nuclear genome of the thylacine.

Miller et al. (2009) found that the thylacine DNA showed a higher degree of postmortem damage than comparable sequences obtained from mammoth hair. This is not surprising, in view of the poorer preservation conditions and higher ambient temperatures experienced by the thylacine specimens. For these reasons, genetic data have been much more difficult to extract from the thylacine than from animals preserved under more favourable conditions. Nevertheless, as the authors indicate, the successful recovery of the thylacine’s mitochondrial genome points towards the feasibility of sequencing the entire nuclear genome of the species in the near future.

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