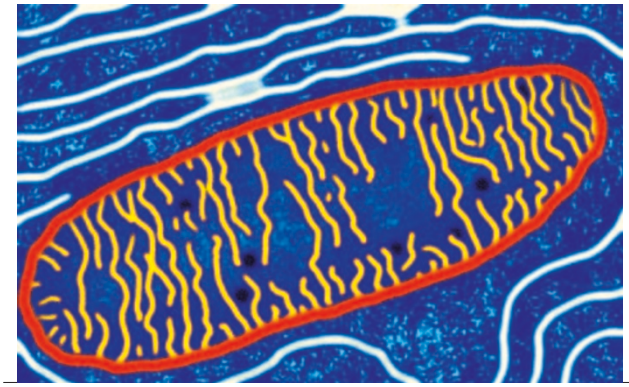

URLs

GENETIC DISEASE

Mitochondria: uncovering the error of their ways

A recent study has revealed a new potential mechanism of mitochondrial mutagenesis, indicating that an unequal distribution of nucleotides might hold the key to some human diseases.

The mitochondrial genome is renowned for playing by its own rules. It has a different structure and mode of inheritance to that of nuclear DNA, and also shows a much faster rate of mutation, with changes occurring up to 100-fold more frequently than in the nuclear genome. This last peculiarity is particularly interesting, as mitochondrial mutations contribute to a range of human diseases, including neurodegenerative disorders, heart conditions and cancer.

Imbalances in the levels of different dNTPs are known to cause replication errors, and previous studies have indicated that such asymmetries might be present in mitochondria. Shiwei Song and colleagues investigated this as a possible cause of increased mitochondrial mutation rates by measuring the levels of individual dNTPs in rat tissues. The balance between the four nucleotides that make up the dNTP pool was significantly different in mitochondria from that in other cell compartments. In particular, whereas dGTP makes up 5–10% of the nuclear pool, it comprises 37–91% of mitochondrial dNTPs.

Is this difference likely to affect mitochondrial mutation rates? To investigate this, the authors tested the fidelity of human mitochondrial DNA polymerase *in vitro* in different dNTP conditions. The enzyme proved to be highly accurate when all nucleotides were present in equal concentrations. However, skewing the pool to represent the situation in mitochondria resulted in a several-fold increase in the rate of replication errors. The types of mistake made by the polymerase were also influenced by the excess dGTP in the mitochondrial pool — A•T to G•C transitions predominated, reflecting an increased tendency for the dGTP to be used incorrectly by the polymerase when its levels are high.

These results fit in well with the mitochondrial mutations that occur in human disorders. In two such diseases — cardiomyopathy and progressive external ophthalmoplegia — A•T to G•C transitions make up 55% and 62%, respectively, of errors in the mitochondrial genome. So, although the cause of the dNTP imbalance remains unknown, this additional peculiarity of mitochondria might provide an important clue to their role in human disease.

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References and links

ORIGINAL RESEARCH PAPER Song, S. *et al.* DNA precursor asymmetries in mammalian tissue mitochondria and possible contribution to mutagenesis through reduced replication fidelity. *Proc. Natl Acad. Sci. USA* 22 March 2005 (doi:10.1073/pnas.0500253102)

FURTHER READING Taylor, R. W. & Turnbull, D. M. Mitochondrial DNA mutations in human disease. *Nature Rev. Genet.* **6**, 389–402 (2005)

WEB SITE

Christopher Mathews' laboratory: http://oregonstate.edu/dept/biochem/faculty/mathews.html