The biology of mitochondrial disease

Mitochondria are subcellular organelles that constitute a metabolic compartment separated from the general cytoplasm by a double layered membrane. The outer membrane serves to regulate access of proteins and metabolites to the mitochondrial compartment, and the convoluted inner mitochondrial membrane is the site of several multicomponent enzyme systems. These include the respiratory chain complexes, which generate the vital ATP through a series of oxidation reactions. Other enzyme systems present within the mitochondria include those of the Krebs cycle (tricarboxylic acid cycle), those involved in part of the urea cycle, and many of the enzymes required for the oxidation of fatty acids and amino acids.

One benefit conferred by the separation of this metabolic compartment from the rest of the cell may be the protection of other cell systems, including nuclear DNA, from oxidative damage by hydroxyl radicals generated during oxidative phosphorylation. This may account for the much greater mutation rate within the mitochondrial genome than in the cell nucleus, leading to either point mutations or rearrangements such as large deletions. The protection from these conferred on the cell by mitochondria may explain not only their evolutionary origin as endosymbionts but also their persistence as discrete organelles within eukaryotes.

In higher organisms, many of the genes encoding enzymatic proteins have become incorporated into the nuclear genome, but a minimal set of genes persists in the very small mammalian mitochondrial genome which could hardly be reduced further without the complete loss of the mitochondrial compartment. The human mitochondrial genome consists of 16 569 nucleotide base pairs encoding the minimal set of genes required for mitochondrial protein synthesis—the bacterial like ribosomal RNA genes and the small set of mitochondria specific tRNA genes—and a few of the protein components of the respiratory chain.

Disorders of mitochondrial function can result from mutations in the nuclear genome, usually inherited as autosomal recessive traits, but defects in the mitochondrial genome display a particularly interesting set of characteristics. When transmitted in a family, such disorders are genome display a particularly interesting set of characteristics. When transmitted in a family, such disorders may vary between tissues in the same person and also with age. The same mutation may therefore be associated in different patients, even members of the same family, with very different clinical manifestations. The mutated copies of the mitochondrial genome may even have a replicative advantage, not just because a deleted mitochondrial chromosome may replicate more rapidly than a full length copy, but also—perhaps—because metabolic stress is more likely in the vicinity of abnormal mitochondria and such stress can trigger mitochondrial replication. There is thought to be an intracellular process of Darwinian selection between mitochondria within the same cell (or syncytium), and a similar competitive process between cells within a tissue. The proportion of mutant DNA will often be substantially greater in terminally differentiated, post-mitotic cell types (for example, neurones, muscle fibres) than in actively dividing cells (for example, lymphocytes). The broad range of phenotypes that can be associated with the same mitochondrial mutation also complicates the recognition of any genotype–phenotype correlations, so that the recognised “symptom clusters” such as MERRF (myoclonic epilepsy and ragged red fibres), MELAS (mitochondrial encephalomyopathy with lactic acidosis), NARP (neuropathic weakness ataxia with retinitis pigmentosa), or LHON (Leber’s hereditary optic neuropathy) are just that—clusters of symptoms that can be caused by a range of different mutations and which overlap with each other clinically.

The A3243G mutation in the mtDNA is renowned for the very wide range of clinical phenotypes with which it has been associated. In this issue, Koga and colleagues report careful studies of this mutation in five separate families ascertained through individuals with contrasting presentations—from Leigh’s syndrome with hypertrophic cardiomyopathy presenting in early childhood to chronic progressive external ophthalmoplegia presenting in middle life. The investigators set out to document the clinical histories of the presenting individuals and their relatives and to determine the degree of heteroplasmy for the A3243G mutation in at least two tissues in each participating family member. Previous reports have correlated the level of heteroplasmy in muscle with clinical severity, and shown that this is a better guide than the level of the mutation in blood lymphocytes, but Koga and colleagues have also examined the DNA from hair follicles and have included many other members of the five families in the study. The results are gratifying—there is indeed a gradient of clinical severity that corresponds both to the proportion of mutant mtDNA and to the results of the other pathological investigations.

While these results are not unexpected, it is important to know that such thorough investigations are compatible with the current model of mitochondrial disease. Further work will be required if the risks of transmission of such mitochondrial disorders are to be clarified and if predictive testing for at risk family members is to give useful results. The proportion of mutant mtDNA in a mother’s lymphocytes is also a poor guide to the level of heteroplasmy in her children—apparently because oocytes derive their 100 000 mitochondria from a very small group of progenitors, a bottleneck. Genetic counselling is difficult because there are few data to guide predictions about the likely severity of disease in a fetus, child, or adult to whom a mitochondrial mutation is transmitted at any given level.
of heteroplasmy. Furthermore, new approaches to mitochondrial genetic disease will be required if we are to intervene successfully and modify the progression of those mitochondrial disorders. What therapeutic agents could reverse the replicative advantage of the defective mitochondria or compensate for the problems with energy metabolism in skeletal and cardiac muscle, the eyes, and the central nervous system? Laboratory work is promising but needs to be translated into clinical results.

ANGUS CLARKE
Senior Lecturer in Clinical Genetics,
University of Wales College of Medicine, Institute of Medical Genetics,
Heath Park, Cardiff CF4 4XN, UK
email: clarkeaj@cardiff.ac.uk


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STAMPS IN PAEDIATRICS

Infectious diseases

The most common infectious diseases which have been featured on postage stamps are tuberculosis, leprosy, smallpox, and malaria. The stamps have been issued to commemorate specific milestones in diagnosis or treatment (for example, Robert Koch and tuberculosis), to raise funds for specific organisations, or to promote international campaigns, such as “The world united against malaria” World Health Organisation campaign of 1962. Other infectious diseases may have appeared on only a single stamp. Leishmaniasis was depicted on the 1985 Kenya stamp to mark the 7th International Congress of Protozoology held in Nairobi from 22–29 June in 1985. The stamp shows an infected patient with cutaneous lesions, and the vector and the life cycle of the organism.
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ANGUS CLARKE

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