

Mitochondria and skin disease

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Summary

In addition to the 3 billion base pair nuclear genome, each human cell contains thousands of copies of a small, 16.5 kb circular molecule of double stranded DNA: mitochondria have their own DNA (mtDNA) which generally accounts for only 1% of the total cellular nucleic acid content. Therefore why should anyone, particularly in the field of dermatology, have an interest in this cytoplasmic organelle and its DNA? This review will address this question; there are three principle reasons: (i) mitochondria have a crucial role both in energy production and the viability of the cell and recently mitochondria have been implicated in programmed cell death (apoptosis). Although much smaller than the nuclear genome, mtDNA is equally important. MtDNA defects and the resulting mitochondrial dysfunction is an important contributor to human degenerative diseases, ageing and cancer; (ii) mtDNA is a significant target of ultraviolet radiation and current work shows that it may be useful as a candidate biomarker of cumulative exposure in skin; and (iii) there is a broad spectrum of skin manifestations that are signs of mitochondrial disorders; in addition, the frequency of skin findings in these syndromes is probably under-reported.

Introduction

Mitochondria are double membrane cytoplasmic organelles devoted to producing 90% of the cells' energy by the process of oxidative phosphorylation and as such have been commonly termed the 'power house of the cell'.¹ Because of their ancestral origin as free-living bacteria-like organisms, mitochondria have their own DNA (mtDNA), a small circular double-stranded molecule containing 37 genes (Fig. 1). MtDNA was discovered 36 years ago and the complete human mtDNA was sequenced by 1981;² however, no mutations were associated with human disease until 1988.³ Since then, more than 50 point mutations and 100 rearrangements (including deletions, depletions and duplications) of the

mitochondrial genome have been associated with human disease⁴ (<http://www.gen.emory.edu/mitomap.html>).

Mitochondrial disorders are often regarded as exclusively neuromuscular but mtDNA defects are involved in a wide range of human diseases including cardiomyopathy, diabetes, cancer, Alzheimer's disease and several other neurodegenerative disorders.⁴⁻⁶ Cellular dysfunction usually occurs when the ratio of mutated : wild-type mtDNA exceeds a threshold level.¹

The respiratory chain within mitochondria is essential for aerobic metabolism and the production of ATP;^{7,8} This multi-subunit pathway results from the complementation of the nuclear and the mitochondrial genome, the latter encoding 13 subunits of the respiratory chain. Mitochondrial disorders can thus result from mutations in either nuclear or mtDNA or in genes controlling the intergenomic 'cross talk' between the mitochondria and the nucleus.¹ Mutations in mtDNA follow a maternal pattern of inheritance.⁴ Recent evidence has shown that during spermatogenesis mitochondria are tagged by the recycling protein ubiquitin; this imprint is a death sentence to the sperm mitochondria which is executed when they

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Accepted for publication 16 December 1999

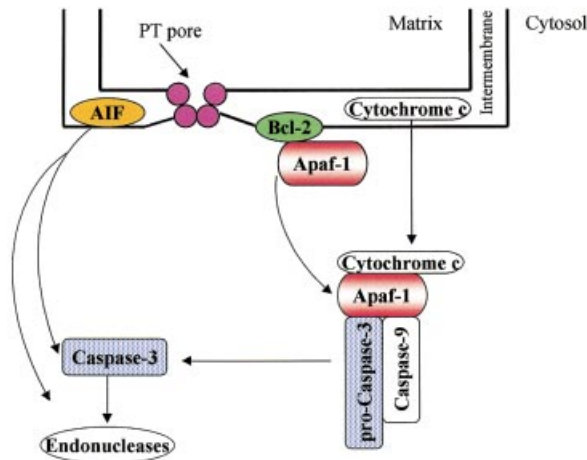


Figure 2 Model for caspase activation by mitochondria. Several different factors are released from mitochondria during apoptosis: AIF (associated with the intermembrane space), Apaf-1 (associated with the outer surface of the mitochondria probably with Bcl-2) and cytochrome c (which is in the intermembrane space). The PT pores occur at contact sites between the inner and outer mitochondrial membrane. AIF directly activates caspase-3 and nuclear endonucleases in the apoptosis process whereas cytochrome c interacts with additional proteins. Caspase-3 cleaves and activates a DNA fragmentation factor that activates endonucleases.

without protective pigmentation is ultraviolet radiation (UVR).¹⁸ Understanding the genetics of the interaction between skin and UVR is important to the understanding of skin cancer susceptibility. Most of the age-associated changes in skin, including the increased incidence of skin cancer, reflect long-term damage induced by photoageing rather than chronological ageing.¹⁹ A major limitation of current studies relating genotype to phenotype of human skin cancer is the absence of reliable markers of exposure to UVR and this is compounded by inter-person differences in the ability to repair photoproducts in nuclear DNA. Several groups have shown that deletions of mtDNA as opposed to nuclear DNA may be useful as a biomarker of UVR exposure.^{20–22} The reasons for this are three-fold.

- The literature agrees that mitochondria are deficient in nuclear excision repair pathways and cannot repair UVR-induced photoproducts such as pyrimidine dimers.^{23–26} Mitochondria however, do show repair of a variety of other DNA damage;^{26,27} confirming that mitochondria possess base excision repair pathways. Repair involving both recombination and mismatch repair²⁸ remains a very controversial area.
- MtDNA has a 10-fold higher mutation rate than nuclear DNA.²⁰

- There are many mitochondrial genomes (2–10 copies) per mitochondrion and many mitochondria per cell (a mammalian cell typically contains 200–2000 mitochondria). As a consequence mitochondrial genomes can tolerate very high levels (up to 90%) of damaged DNA through complementation by the remaining wild-type mtDNA.²⁹

Direct evidence for the production of UV-induced thymine dimers in purified mtDNA³⁰ has shown mtDNA to be a significant target of UVR. Indirect evidence has shown an increased frequency of single mtDNA deletions (usually the 4977 bp common deletion which spans the ATPase8 to ND5 genes; Fig. 1) with increasing UVR exposure;^{20,22,31} However a major limitation of these indirect studies is the focus on the frequency of a single mtDNA deletion which represents only the ‘tip of the deletion iceberg’.³² These studies have therefore been extended by using a long-range PCR technique to amplify almost the entire 16 569 bp mitochondrial genome to determine the complete spectrum of mtDNA deletions secondary to UVR exposure in human skin.³³ This study showed that there was a significant increase in the number of deletions with increasing UVR exposure in the epidermis. Importantly these findings were not confounded by the well-known age-dependent increases in mtDNA deletions that have been observed in various cell types³⁴ including skin.³⁵ Furthermore, in the first quantitative study of the common deletion in human skin²² it was clearly shown that high levels (> 1%, and even up to 22%) of deletions are associated with photoageing whereas, by contrast, low levels (< 1%) are associated with chronological ageing. These values for chronological ageing agree with those described in other cell types which typically range from 0.001 to 1%.³⁴

The spectrum of skin manifestations associated with mitochondrial disorders

Approximately 90% of the oxygen consumed within a eukaryote is used in mitochondrial respiration and so the metabolic rate of a cell, and indeed tissue, is related to mitochondrial function.³⁶ Post-mitotic tissues such as the brain, muscle and heart have high levels of mitochondria, which results in a special vulnerability of these tissues to mitochondrial dysfunction. Mutations of the mtDNA can result in a variety of clinical presentations that are primarily restricted to tissues with high levels of mitochondria. Pathological conditions which can be caused by mtDNA mutations include myopathy, ophthalmoplegia, dilated or hypertrophic cardiomyopathy, lactic acidosis, encephalopathy, diabetes mellitus, stroke

Table 1 Mitochondrial DNA diseases: some of the disorders that can be caused by mutations in mtDNA.

Disorder	Features
CPEO (Chronic progressive external ophthalmoplegia)	Paralysis of eye muscles and mitochondrial myopathy (see below)
Dystonia	Abnormal movements involving muscular rigidity; frequently accompanied by degeneration of the basal ganglia of the brain
KSS (Kearns–Sayre syndrome)	CPEO combined with such disorders as retinal deterioration, heart disease, hearing loss, diabetes and kidney failure
Leigh's syndrome (or subacute necrotizing encephalopathy)	Progressive loss of motor and verbal skills and degeneration of the basal ganglia of the brain
LHON (Leber's hereditary optic neuropathy)	Permanent or temporary blindness stemming from damage to the optic nerve
MELAS (mitochondrial encephalomyopathy, acidosis and stroke-like episodes)	Dysfunction of brain tissue (often causing seizures, transient regional paralysis and lactic dementia) combined with mitochondrial myopathy(see below) and a toxic build-up lactic acid in the blood
MERRF (myoclonic epilepsy and ragged red fibres)	Seizures combined with mitochondrial myopathy (see below); may involve hearing loss and dementia
Mitochondrial myopathy	Deterioration of muscle, manifested by weakness and intolerance for exercise, muscle often displays ragged red fibres, which are sub-sarcolemmal accumulation of mitochondria that histologically stain red
NARP (neurogenic muscle weakness, ataxia and retinitis pigmentosa)	Loss of muscle strength and co-ordination, accompanied by regional brain degeneration and deterioration of the retina
Pearson's syndrome	Childhood bone marrow dysfunction and pancreatic failure; those who survive often progress to KSS

and deafness^{4:37,38} (Table 1). MtDNA has the capacity to exist as a mixture of both wild-type and mutant mtDNA genotypes within a cell, a phenomenon known as heteroplasmy. This results in a remarkable pleiotropy of disease phenotype; in addition, a variable distribution of mutant mtDNA can occur between the tissues of an affected individual.

The frequency of skin findings in mitochondrial disorders is unknown, although recently there have been two major studies which have explored this question. One study reviewed 274 cases of mitochondrial syndromes reported in the literature for skin manifestations.³⁹ The second involved the direct investigation by the same physicians of 140 children with mitochondrial disorders.⁴⁰ In addition, a review of the current literature revealed other reports of mitochondrial disorders with skin manifestations.^{38,41–48} Taken together, the skin findings can be divided into six categories as detailed below in descending order of frequency of observation:

- lipomas;^{39,44–46}
- disorders of pigmentation and erythema;^{38–40,42}
- alopecia and hair shaft abnormalities^{39,40}
- acrocyanosis;^{39,40}
- hypertrichosis;^{39,40} It is interesting to note that a high frequency of hypertrichosis (10/12 patients) has been observed in a study of those patients with a mitochondrial disease called Leigh syndrome which has been caused by a mutation in the nuclear gene

SURF 1 (D. Thorburn, Melbourne, Australia, personal communication);

- other skin disorders including palmoplantar keratoderma (linked with deafness),⁴⁸ anhidrosis,⁴³ purpuric lesions⁴¹ and dermatomyositis.⁴⁷

With the exception of lipomas, the frequency of skin findings in mitochondrial disorders described in the studies by Flynn *et al.* and Bodemer *et al.* was 10% and 6%, respectively. The latter study is likely to underestimate the true incidence of skin findings simply because patients with mitochondrial disorders are unlikely to be investigated primarily by a dermatologist. Although the relationship between mtDNA defect, mitochondrial dysfunction, clinical syndrome and skin manifestation remains unclear it is likely that skin manifestations are attributable to mitochondrial disorders and should be considered as belonging to the broad spectrum of presenting symptoms.

Conclusion

The ubiquitous nature of mitochondria and the crucial role that mitochondria have in energy metabolism, together with the fact that mtDNA has been involved in a myriad of human disease processes, suggest that mitochondria are too important to ignore as highlighted in a recent issue of *Science* dedicated to this organelle (Fig. 3). Within dermatological research mtDNA appears



Figure 3 Pancreatic cell mitochondrion (approximately 2 μm in length). This image highlights the organelle's highly folded inner membrane. Image reprinted, with permission, from the cover of *Science*, 5th March 1999 volume 283; copyright (#porter 991294) American Association for the Advancement of Science.

to be a good candidate biomarker of cumulative UVR exposure in human skin. In addition, the frequency of skin manifestations in mitochondrial disorders is probably under-reported because of a lack of clinical awareness.

Acknowledgements

I thank Dr N. J. Reynolds for his helpful comments on this manuscript.

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Key points

- Mitochondria have a crucial role both in energy production and cell viability but also in the process of apoptosis.
- Mitochondrial DNA defects occur in many different tissues and mitochondrial disorders are involved in a myriad of human disease processes including cancer, neurodegeneration, diabetes and ageing.
- Mitochondrial DNA can be used as a biomarker of cumulative UVR exposure in skin.
- There is a broad spectrum of skin manifestations in mitochondrial disorders, the frequency of which is probably under-reported.
- Given the complexity of mitochondrial genetics and biochemistry the clinical manifestations of mitochondrial disorders are extremely heterogeneous.