Inherited mitochondrial disease

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Abstract

Inherited disorders that affect mitochondrial function are an exceedingly diverse group of conditions with different pathophysiological mechanisms and highly variable clinical phenotypes. Paediatric patients may present with a defined clinical syndrome or, more commonly, with non-specific signs of mitochondrial disease. Recognition of mitochondrial disease relies on having a high index of suspicion when faced with a multisystem disorder of unclear aetiology, in addition to knowledge of the various defined mitochondrial clinical syndromes. However, diagnosis remains a particular challenge, owing to the lack of sensitive and specific biomarkers. Evidence of mitochondrial dysfunction should be sought from a variety of organ systems using both functional and biochemical testing, although recent advances in genomic technology are changing the approach to diagnosis. Treatment of mitochondrial disease also presents a significant challenge, since although a few disease specific therapies exist, treatment remains predominantly supportive. Some cofactors, vitamins and antioxidants are commonly used to enhance mitochondrial function, although there is little evidence to support their efficacy.

Keywords diagnosis; investigation; mitochondrial disease; multiorgan; treatment

Introduction

Mitochondria are important intracellular organelles that are ancient additions to the early eukaryotic cell, originating from the fusion of a proteobacterium with a eukaryotic precursor. The advent of mitochondria is proposed to herald the evolutionary expansion of eukaryotes, and over time the form and function of the mitochondria have changed considerably. While they have retained a double membraned structure, many functions have become integrated with the host cell. The extent of this integration can be illustrated by considering the nature of mitochondrial DNA (mtDNA), which is distinct from nuclear DNA (nDNA) and resides within the mitochondria. In humans it encodes for just 13 mitochondrial proteins (and 24 RNA species), a fraction of the total number of mitochondrial proteins which number over 1500; the remainder are encoded by nuclear genes.

Mitochondria are the main source of ATP in the eukaryotic cell, which is produced by oxidative phosphorylation that in turn is driven by an electrochemical gradient created by the respiratory chain. Their role in energy production and homeostasis is critical to cell function, but many other cellular functions also occur within the mitochondria including those essential to cellular signalling and apoptosis. Mitochondria exist in varying numbers dependent on cell type and form a network of interconnecting organelles (a notable exception is erythrocytes that lack mitochondria).

Inherited defects of mitochondrial function manifest in a notoriously diverse manner, with clinical features classically described as occurring 'in any organ or tissue, at any age and with any mode of inheritance'. The pathophysiology of mitochondrial disease is complex and remains poorly understood. Historically these conditions were termed 'respiratory chain defects' as mitochondrial research focused on unravelling the complexity of the respiratory chain. The advent of modern techniques such as proteomics and next-generation genomics has facilitated the discovery of defects in disparate mitochondrial functions. Primary defects of mitochondrial function have been described in the respiratory chain (five complexes, ~90 polypeptides), mtDNA replication and translation, respiratory chain cofactor synthesis, protein/solute import and in mitochondrial membrane structure and function (Figure 1). Secondary mitochondrial dysfunction has been implicated in a variety of disease states such as Alzheimer's, Huntingdon's, cancer and also in the aging process. This article will focus on primary inherited conditions of mitochondrial dysfunction.

When to suspect mitochondrial disease

The diverse nature of mitochondrial disease leads to a significant diagnostic challenge. Crucial to the recognition of mitochondrial disease is its multisystem nature, which may lead to several organ systems being affected. Examples of these clinical features are summarised in Table 1. Although many patients have an unspecific combination of symptoms (non-syndromic forms), there is an ever-growing number of defined clinical syndromes (Table 2) whose recognition can expedite diagnosis. However, the majority of paediatric patients investigated for mitochondrial disease do not fall into the syndromic category. The presence of unexplained lactic acidosis often leads to the consideration of mitochondrial disease, but lactate is neither a sensitive nor specific marker of mitochondrial disease.

Obtaining a family history is important in the investigation of inherited metabolic disease, and mitochondrial disease is no exception. However, any pattern of inheritance can be observed in mitochondrial disease. Disorders resulting from defects in genes encoded in the nuclear genome can be inherited as autosomal recessive or dominant or X-linked traits, while disorders of the mitochondrial genome may be maternally inherited or be sporadic. Further complicating the inheritance of the mitochondrial genome is the concept of heteroplasmy. There are varying numbers of mitochondrial genomes within each cell depending on cell-type, with somatic cell lines commonly having around 1000 copies. Thus cells can contain a mixture of mutated and wild-type mtDNA, a state known as heteroplasmy. In some mitochondrial disorders, the amount of heteroplasmy can be correlated with clinical phenotype, for example m.8993T>G mutation causes NARP (late onset neuropathy, ataxia and retinitis pigmentosa) in low copy number while in high copy number

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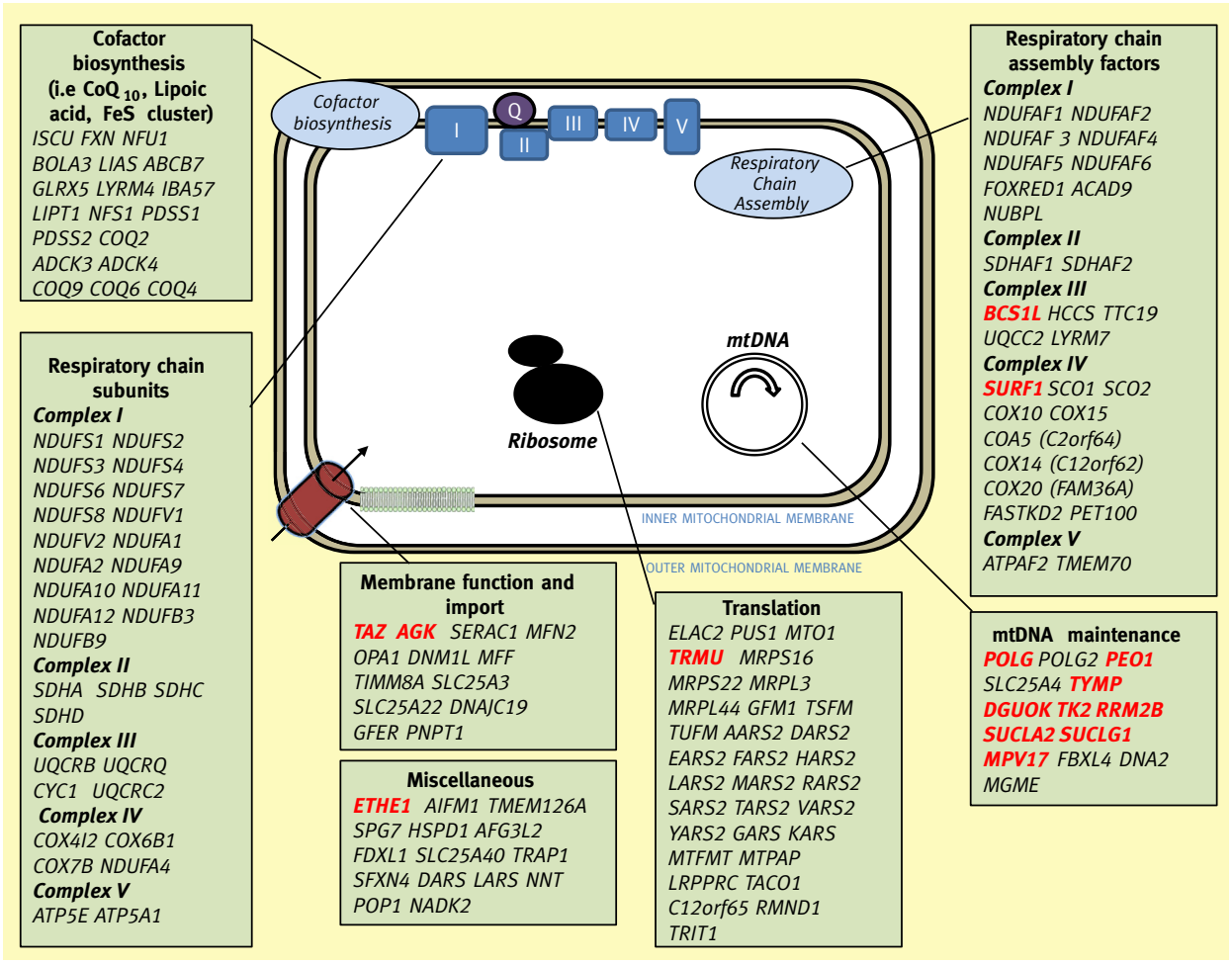

Figure 1 Inherited disorders affecting different components of mitochondrial function: Respiratory chain, either individual complex subunits or assembly factors; mtDNA replication and maintenance; mtDNA transcription; mitochondrial translation; import of proteins/solutes; membrane structure and function; cofactor synthesis. Nuclear genes implicated in mitochondrial disease are shown (those in red are discussed within text).

cause infantile encephalopathy (maternally inherited Leigh syndrome). The inheritance of mtDNA from ovum to embryo is poorly understood, but a genetic bottleneck causes the degree of heteroplasmy passed from the mother to offspring to be unpredictable.

Defined clinical syndromes

A comprehensive list of all known mitochondrial syndromes is not within the scope of this article. Some examples of the more common syndromes, those with different pathological mechanisms and those conditions whose diagnosis will drastically alter management are described below. A broader list of clinical syndromes can be seen in Table 2.

Leigh syndrome

Leigh syndrome (subacute necrotising encephalomyelopathy) is probably the most commonly recognised mitochondrial disorder in childhood. Neurological features such as psychomotor retardation, dystonia, ophthalmoplegia and ataxia predominate, variably accompanied by systemic features such as faltering growth, anaemia, cardiomyopathy and diarrhoea. The disorder commonly has a relapsing and remitting neurological course, although some patients may remain stable for many years whilst others display a rapid progressive deterioration. The characteristic changes in the brain comprise of focal, bilateral and symmetrical lesions in the thalamus, brain stem and posterior columns of the spinal cord (Figure 2). The aetiology of Leigh syndrome is heterogeneous and includes various enzyme deficiencies, including defects of respiratory chain complexes I and IV, pyruvate dehydrogenase (PDH), biotinidase, coenzyme Q_{10} synthesis and numerous mtDNA mutations (most frequently in genes encoding subunits of complex V and complex I). A significant proportion of those that have complex IV (cytochrome oxidase, COX) deficiency have mutations in *SURF1*, a nuclear-encoded gene responsible for the assembly of COX and the most common nuclear cause of Leigh syndrome. Inheritance of Leigh syndrome may be maternal (mtDNA mutations), autosomal recessive (e.g. SURF1 deficiency) or X-linked (e.g. PDH deficiency), so without a definitive genetic diagnosis genetic counselling is challenging.

Mitochondrial DNA depletion syndrome (MDDS)

A number of different clinical syndromes result from a deficiency of mtDNA replication or repair, all of which are caused by defects