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REVIEW ARTICLE

Mitochondrial Dysfunction in Neurodegenerative Diseases

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Abstract Mitochondria play a pivotal role in mammalian cell metabolism, hosting a number of important biochemical pathways including oxidative phosphorylation. As might be expected from this fundamental contribution to cell function, abnormalities of mitochondrial metabolism are a common cause of human disease. Primary mutations of mitochondrial DNA result in a diverse group of disorders often collectively referred to as the mitochondrial encephalomyopathies. Perhaps more importantly in numerical terms are those neurodegenerative diseases caused by mutations of nuclear genes encoding mitochondrial proteins. Finally there are mitochondrial abnormalities induced by secondary events e.g. oxidative stress that may contribute to senescence, and environmental toxins that may cause disease either alone or in combination with a genetic predisposition.

Keywords Mitochondria · Mitochondrial DNA · Genes Parkinson's disease · Friedreich's ataxia · Oxidative stress

Introduction

Over the last 20 years there has been an increasing recognition of the role played by the mitochondrion in causing human diseases [1–3]. These are mediated through mutations of mitochondrial DNA (mtDNA), nuclear DNA genes encoding mitochondrial proteins and endogenous and exogenous toxins that target mitochondrial metabolism. These diseases can affect any organ although muscle and nerve are most frequently involved. This review will focus upon mitochondrial dysfunction in selected neurodegenerative diseases.

Special issue article in honor of Dr. Anna Maria Giuffrida-Stella.

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Chronic Progressive External Ophthalmoplegia and Kearns-Sayre Syndrome

Chronic progressive external ophthalmoplegia (CPEO) is predominantly a myopathic disorder but there have been reports of dementia, seizures, myoclonus and stroke like episodes [4, 5]. In Kearns Sayre syndrome (KSS), CPEO is accompanied by pigmentary retinopathy, and one or more of complete heart block, a cerebrospinal fluid (CSF) protein level of above 1 g/l, and ataxia [6]. The diagnostic criteria quote an age of onset below 20 years, but improved identification of cases has revealed later onset in some patients.

Mitochondrial DNA from CPEO/KSS patients shows large single deletions detectable in DNA extracted from muscle samples, but blood mtDNA analysis usually is normal. These deletions are found in 80% of those with KSS, and 70% of those with CPEO [7–9]. Histological examination of muscle reveals ragged red fibres (RRFs) and a mosaic pattern of cytochrome oxidase (COX) negative fibres. Deletions probably arise de novo during oogenesis in the mother and patients with mtDNA deletions therefore present as sporadic cases [10]. The risk of transmission of deletions is approximately 4% and it is rare for more than one sibling to be affected.

Encephalomyopathies

The common mitochondrial encephalopathies include MELAS (myopathy, encephalopathy, lactic acidosis and

stroke-like episodes) and MERRF (myoclonic epilepsy and ragged red fibres). MELAS can include psychomotor retardation, ataxia, cognitive impairment, deafness, diabetes mellitus and limb weakness. Of all cases meeting the clinical criteria for MELAS, 80% are positive for an A to G transition at base pair 3243 within the *tRNA Leu*^{UUR} gene [11–13].

The core clinical features of MERRF are myoclonus, ataxia, and seizures. Myoclonus is often the presenting symptom, and may be induced by action, noise, or photic stimulation. Seizure types are variable, but include drop attacks, focal seizures, and photo-sensitive tonic-clonic seizures [14, 15]. Myopathy is usually either mild, subclinical, or absent. RRFs are seen on muscle biopsy in the majority of patients, but not in all cases. Additional features include ophthalmoplegia, ptosis, deafness, peripheral neuropathy, headache, foot deformity, optic atrophy and cervical lipomas. The most commonly detected mutation, found in approximately 80% of cases fulfilling the clinical criteria for MERRF, is at position 8344 within the *tRNA Lys* [11, 16, 17].

Neurogenic Weakness Ataxia and Retinal Pigmentation (NARP)

The key features of NARP are peripheral neuropathy, ataxia, retinitis pigmentosa, seizures and dementia [18]. A spectrum of neurological findings have been described in NARP including migraine and mental retardation [18–24]. Clinical features are variable as is the age of onset which in one series varied between 1 and 32 years [25, 26]. Inheritance is maternal.

The commonest mutation is a T to G transversion at nucleotide position 8993. This causes a change from the highly conserved leucine to arginine within subunit 6 of the mitochondrial F_0F_1 ATP synthase. Patients with NARP usually have above 80% mutant mtDNA levels. With mutant mtDNA levels below 75% patients usually suffer from pigmentary retinopathy alone, or suffer migraines, or are asymptomatic [18–23]. Ragged-red fibers and other morphological mitochondrial hallmarks are lacking in muscle biopsies from patients with NARP [18].

Leigh Syndrome (LS)

Leigh syndrome (LS) is a subacute necrotising encephalomyelopathy characterised by bilateral symmetrical focal necrotic lesions within the thalamus, extending into the pons, inferior olives and spinal cord. The clinical features of LS are of psychomotor retardation, hypotonia, failure to thrive, respiratory abnormalities, oculomotor disturbances, ataxia, optic atrophy, seizures and lactic acidosis. Biochemical abnormalities include defects of oxidative phosphorylation [27] (in particular complex I [28] or complex IV [29, 30], and deficiency of the pyruvate dehydrogenase complex [31] and biotinidase deficiency [32]. The majority of LS cases are believed to result from nuclear gene defects [33, 34]. This has been confirmed for cases of LS with PDH complex deficiency [33], complex I [35], and II [36]. Complex IV deficient LS results from mutations of the *Surf* or other assembly genes [37–39]. Up to 20% of LS patients have the T to G, or T to C, mtDNA mutation at position 8993 within the *ATPase 6* gene of complex V [40–44]. Mutant loads are above 90%, and lower levels of this mutation are associated with the NARP syndrome. Other mtDNA mutations have been described including base substitutions, deletions and depletion of mtDNA levels [45–48].

Friedreich's Ataxia

Friedreich's ataxia (FRDA) is an autosomal recessive disease characterised clinically by a progressive gait and limb ataxia, absence of deep tendon reflexes and loss of position and vibration sense in the lower limbs. Skeletal abnormalities including kyphosis, hypertrophic cardiomyopathy and less commonly, diabetes and optic atrophy are also present in FRDA patients.

Over 95% of FRDA patients have a homozygous expansion of a GAA triplet repeat (6–34 GAA repeats in controls expanded to between 67 and 1700 in patients) in intron 1 of the *frataxin* gene on chromosome 9 [49]. Most of the remaining patients are compound heterozygotes with the GAA expansion in one allele and point mutations in the other [50]. No patient has yet been described with a point mutation in each allele.

Defects of the mitochondrial respiratory chain have been demonstrated in yeast YFH1 mutants [51, 52], conditional frataxin knockout transgenic mice [53] and post mortem heart and skeletal muscle from FRDA patients [54, 55]. The pattern of respiratory chain dysfunction (complexes I, II and III) is similar to that caused by oxidative stress caused and knockout of manganese superoxide dismutase [56], or secondary to excitotoxicity in Huntington's disease [57]. However, all the enzyme activities decreased in FRDA contain Fe–S clusters which led to the proposal that an abnormality of Fe–S cluster synthesis may be responsible for these defects.

^{31}Phosphorous magnetic resonance spectroscopy (^{31}P MRS) is an in vivo technique that can measure high energy phosphorous compounds (phosphocreatine and ATP) in heart and skeletal muscle. In skeletal muscle phosphocreatine (PCr) levels fall during exercise, and the analysis of the rate at which PCr levels recover following exercise (Vmax) is a measure of the efficiency of oxidative

phosphorylation [58]. The PCr/ATP ratio is used as a good measure of energy availability in heart. ^{31}P MRS analysis of FRDA patients revealed markedly decreased oxidative phosphorylation in the heart [59] and skeletal muscle, with the latter correlating with the size of the smallest GAA repeat [60]. These data underline the role of mitochondrial dysfunction in FRDA and suggest it is playing a primary role in disease pathogenesis [61].

Vitamin E is a naturally occurring lipid soluble antioxidant distributed throughout cellular membranes and is particularly abundant in mitochondrial membranes. The treatment of FRDA patients with vitamin E has only been reported in conjunction with coenzyme Q10. We have assessed the efficacy of long term treatment of 10 patients with FRDA with high doses of vitamin E (2100 IU/day) and coenzyme Q10 (400 mg/day). After 6 months ^{31}P MRS data indicated that heart and skeletal muscle energetics were significantly improved [62]. Four year follow up data from this study showed the enhanced energy levels were maintained, clinical parameters were stabilised or improved in 7 out of 10 patients and heart fraction shortening had improved [63]. This effect of vitamin E is supported by the consequences of vitamin E deficiency on mitochondrial function [64].

Idebenone is a short chain analogue of coenzyme Q10, is well tolerated by humans, crosses the blood brain barrier, has been reported to be a relatively good antioxidant [65], and has been used in a variety of diseases with some benefits [66, 67]. The effect of idebenone upon cardiac hypertrophy in FRDA patients was assessed using echocardiography, but other clinical improvements were not reported. After 6 months treatment cardiac hypertrophy was decreased in up to half the patients tested, although this was not always associated with improved fraction shortening [68].

Parkinson's Disease

A mitochondrial defect in PD was first identified in 1989 in substantia nigra from patients with PD [69–73]. These study has been expanded over the years and results to date show that there is about a 35% complex I deficiency in PD nigra [74]. This defect in complex I activity does not affect any other part of the respiratory chain an unusual feature of mitochondrial disease [75]. In addition, no defect in mitochondrial activity has been identifiable in any other part of PD brain, including caudate putamen, globus pallidus, tegmentum, cortex, cerebellum or substantia innominata [76].

The discovery of complex I deficiency in PD raised issues regarding its role in terms of whether it played a primary or secondary part in pathogenesis. The PD brains examined were from patients with longstanding disease who had also been treated with a variety of drugs e.g. levodopa. However, there was no deficiency of complex I activity in PD striatum which one might expect from the rat model of levodopa toxicity [77]. Furthermore, patients with multiple system atrophy who have taken L-dopa in quantities and for duration comparable to patients with PD have no defect of mitochondrial activity in their substantia nigra [78]. Other drugs such as dopamine agonists and monoamine oxidase B inhibitors are not known to influence complex I activity.

Following the report of complex I deficiency in PD substantia nigra, respiratory chain abnormalities were described in skeletal muscle mitochondria from PD patients. This particular area has proved very contentious, with several groups either describing similar defects, or no abnormality [78, 79, 80]. Finally, mitochondrial complex I deficiency was also identified in platelet mitochondria of PD patients [81, 82].

Several studies have investigated the structure of mtDNA in tissues from PD patients to determine whether the complex I defect is associated with an underlying mtDNA mutation [83]. No reproducible abnormality of mtDNA has been identified in PD. However, the level of mtDNA deletions in single substantia nigral neurons appears to increase substantially over the age of 65 years [84]. One study found a high proportion of deleted mtDNA ($43 \pm 9.3\%$) in nigral neurons of controls and a higher proportion in parkinsonian nigra ($52.3 \pm 9.3\%$). These results confirm that the human substantia nigra is a site of free radical mediated damage to mtDNA and that this is enhanced in neurodegenerative diseases.

Two studies have used genetic transplantation to investigate the potential for PD mtDNA to determine the complex I defect. In one, unselected PD platelets were fused and grown in mixed culture [85]. In another, PD patients were selected on the basis of demonstrating a peripheral complex I deficiency. These patients' cells were then fused with rho-zero cells and grown both in mixed and clonal culture [86]. In both, mtDNA transferred from the PD patients induced a complex I defect in the recipient cybrid cells. These results indicate that the mtDNA in these patients caused the complex I deficiency through either inherited or somatic mutations. Further experiments suggested that the recipient cells also developed abnormal calcium handling and a lower mitochondrial membrane potential.

MtDNA *polymerase gamma (POLG)* mutations have been demonstrated in patients with progressive external ophthalmoplegia (PEO) and parkinsonism [87].

The human *POLG* gene includes a trinucleotide microsatellite CAG repeat that encodes a polyglutamine tract in the amino-terminal region of the POLG protein. Although expansion of CAG repeats are a cause of several neurodegenerative diseases no changes were seen in the CAG repeat of PD patients that might have contributed to modifications of mtDNA [88].

Recessive mutations in *PINK1* were found to be responsible for a familial form of early-onset parkinsonism, previously mapped to chromosome 1p36 (the PARK6 locus) [89]. *PINK1* mutations are relatively rare. The *PINK1* gene is ubiquitously transcribed and encodes a mitochondrial kinase [90]. Preliminary data have suggested that PINK1 may play a role in protecting cells against stress conditions that affect mitochondrial membrane potential, but the downstream targets through which PINK1 mediates its protection have not been identified. *Parkin* mutations are an uncommon cause of autosomal recessive PD. There is some evidence to implicate mitochondrial dysfunction in the pathogenesis of *parkin* mutations. One report has shown that parkin may be localised within mitochondria [91]. Parkin was present within the mitochondrial matrix in proliferating cells and entered the cytosol when the permeability pore was open. This extra-mitochondrial localisation was also seen in differentiated cells. Up-regulation of parkin resulted in an increase in mtDNA transcription and translation via an interaction with mitochondrial transcription factor A, while RNA silencing of parkin lead to a reduction of levels. It is notable that parkin over-expression can compensate for PINK1 mutations in Drosophila [92, 93]. The implication is that parkin functions downstream of PINK1 and intervenes in the pathogenetic pathway of PINK1 mutations.

Mutations in *DJ1* are another rare cause of early onset autosomal recessive PD [94]. DJ1 is a widely expressed cytoplasmic 23 kDa protein that is distributed in several subcellular compartments including the mitochondrial matrix and inter-membranous space [95]. DJ1 is thought to function as an anti-oxidant protein. There is some evidence that the distribution of DJ1 may be modified by mutations and that this leads to decreased nuclear and increased mitochondrial localisation which in turn results in impaired transcriptional co-activator function rendering cells more sensitive to pyrimidine binding tract protein-associated splicing factor (PSF) induced apoptosis [96].

Mutations in the *Omi/HTRA2* gene have been identified in four PD patients with an additional mutation thought to represent a risk factor for PD [97]. The Omi/HTRA2 protein is a mitochondrial protein located within the inter-membranous space and functions as a procaspase, released as part of the apoptotic cascade. The G399S mutation results in reduced serine-protease activity. *Omi/HTRA2* knockout mice display a parkinsonian phenotype that includes rigidity but additional features that include ataxia muscle wasting and premature death [98].

The benefits of an improved understanding of the mitochondrial involvement in the pathogenesis of PD has already translated into potential therapeutic interventions to slow progression of the disease [99].

Mutations have likewise been found in nuclear genes encoding mitochondrial proteins in neurodegenerative diseases such as chromosome 16-linked hereditary spastic paraplegia (*paraplegin*), autosomal dominant optic atrophy (*OPA1*) and Charcot Marie Tooth disease (*mitofucin*) [100]. Severe defects of complexes II and III of the respiratory chain have also been described in Huntington's disease brain [101, 102]. The relevance of the latter has been highlighted by the recent observation that mutant huntingtin reduces the expression of the peroxisome proliferator-activated receptor-γ co-activator 1α (PGC-1α) [103]. This protein controls many metabolic processes including mitochondrial biogenesis and oxidative phosphorylation by the regulation of expression of proteins of the respiratory chain.

Conclusions

Mitochondria undoubtedly play an important role in human pathology and there is little doubt that numerous other disorders will be attributed to mitochondrial dysfunction. The difficulty is in finding appropriate treatments. Targeting the mitochondrion with suitable drugs may become an important focus for future therapeutic approaches.

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