ELSEVIER

Biochimica et Biophysica Acta 1410 (1999) 99–102

BIOCHIMICA ET BIOPHYSICA ACTA
BBA

Editorial

Mitochondrial disorders

A.H.V. Schapira *

University Department of Clinical Neurosciences, Royal Free and University College Medical School, Rowland Hill Street, London NW3 2PF, UK

Abnormalities of mitochondrial metabolism causing human disease have been recognised for more than 30 years. They encompass defects of fatty acid oxidation, tricarboxylic acid cycle enzymes and the respiratory chain and oxidative phosphorylation (OXPHOS) system. The first mutations of mitochondrial DNA (mtDNA) were described 10 years ago: in excess of 80 mtDNA mutations have now been associated with a considerable spectrum of human disorders. As mtDNA encodes proteins of the OXPHOS system, such mutations frequently result in a deficiency of one or more of the constituent enzymes (complexes I–V). Inevitably, respiratory chain defects are the main focus of attention in mitochondrial diseases as they represent by far the commonest known biochemical deficiency of mitochondrial metabolism causing disease. The study of mitochondrial metabolism has recently included neurodegenerative diseases, specifically Parkinson's disease (PD), Huntington's disease (HD) and Alzheimer's disease (AD). OXPHOS defects have been described in all these three. Although their relationship to aetiology in PD and AD remains undefined, they are likely, at least in PD, to contribute towards pathogenesis of neuronal cell death. This topic, and the role of mitochondria in apeptosis, are reviewed in this issue by Olanow and Tatton, and by Schapira. The recent characterisation of the protein products involved in Friedreich's ataxia (FA), hereditary spastic paraplegia (HSP) and hepatolenticular degeneration (Wilson's disease) as nuclear encoded mitochondrial proteins has broadened the spectrum of 'mitochondrial disorders' still further. OXPHOS defects have been identified in FA and HSP, but not yet in Wilson's disease. The complexity of factors that may affect respiratory chain function now requires that they be reclassified in order to introduce some consistency of nomenclature and improve our understanding of the different mechanisms affecting OXPHOS. A new classification is outlined in Table 1.

Primary OXPHOS defects are thus defined as those caused by mutations of mtDNA or nuclear genes encoding subunits of complexes I–V. The latter may include mutations affecting mitochondrial targeting of the protein, i.e. the N-terminus leader sequence. Only two nuclear encoded mutations have been defined to date [1,2]; a further defect in the import of the Rieske iron sulphur (FeS) centre has been postulated, but not defined at the molecular level [3]. As discussed by J.A. Morgan-Hughes and M. Hanna in this issue, a multitude of different mtDNA mutations have been reported including those involving tRNAs and protein coding genes of complexes I, IV and V as well as cytochrome *b*. The majority of mtDNA mutations involve tRNA genes either as point mutations or as large scale deletions. One mutation at bp 1555 in rRNA has been associated with nonsyndromic deafness and in determining susceptibility to aminoglycoside induced deafness. Although new mtDNA mutations will continue to be described, the real challenge is to understand the pathogenesis of these mutations. Nuclear background appears to have some influence on the drift of mutation expression [4] as well as on biochemical expression [5]. Respiratory chain deficiencies may

* Fax: +44 (71) 431-1577; E-mail: schapira@rfhsm.ac.uk

0005-2728/99/$ – see front matter © 1999 Elsevier Science B.V. All rights reserved.
PII: S0005-2728(98)00160-1

Table 1

Class I: primary OXPHOS defects		
These involve mutations of mtDNA genes or nuclear genes resulting in impaired activity of complexes I–V, e.g.		
a.		Mutations of mtDNA:
	i.	large scale deletions, duplications involving protein coding genes and tRNA genes;
	ii.	mutations of protein coding genes, e.g. point mutations, small rearrangements;
	iii.	mutations of tRNA and rRNA genes.
b.		Mutations of nuclear genes encoding OXPHOS subunits. These would include mutations affecting the gene promoter, the mature protein or its targeting sequence.
Class II: secondary OXPHOS defects		
a.		Genetic:
	i.	abnormalities of mtDNA induced by nuclear gene defects affecting mtDNA transcription, translation or replication, e.g. autosomal dominant or recessive multiple deletions, or mtDNA depletion;
	ii.	direct damage to mtDNA or defects of mtDNA repair, e.g. frataxin deficiency and oxidative damage in Friedreich's ataxia;
	iii.	defects of the import pathway of nuclear encoded OXPHOS subunits, e.g. membrane receptors, processing proteins, etc.;
	iv.	defects of the assembly of OXPHOS, e.g. chaperone mutations, defects of haem synthesis.
b.		Toxic:
	i.	endogenous, e.g. free radicals including superoxide, nitric oxide, peroxynitrite;
	ii.	exogenous, e.g. methyl-4-phenyl 1,2,3,6 tetrahydropyridine, 3-nitropropionic acid, malonic acid, isoquinolines.

also result in increased generation of free radicals as well as act to lower the apoptotic threshold of cells. However, much remains to be understood in terms of the mutational load for biochemical expression and the mechanisms of cell failure.

Secondary OXPHOS deficiencies encompass genetic and environmental factors. Certain abnormalities of mtDNA have been shown to be secondary to nuclear mutations. Autosomal dominant chronic progressive external ophthalmoplegia (CPEO) has been mapped to loci on chromosome 3 or 10 in some families whilst other families are linked to neither. Affected patients have multiple mtDNA deletions. These contrast with the single mtDNA deletions found in patients with sporadic CPEO. mtDNA depletion is characterised by onset in infancy of, usually, liver and renal failure with lactic acidosis. mtDNA levels in affected tissues may be less than 1% of control. When the depletion is expressed in culture, enucleation and fusion with control mtDNA-less (ρ^0) cells results in restoration of mtDNA levels – clearly implying that the primary defect lies in nuclear DNA. The role of transacting factors on mtDNA transcription, translation and replication and their possible involvement in mtDNA depletion are elegantly and comprehensively reviewed in this issue by J.-W. Taanman.

Frataxin and paraplegin deficiencies are good examples of secondary OXPHOS deficiency. Both are mitochondrial proteins, and cause FA and chromosome 16-linked HSP respectively. Frataxin deficiency, caused by an expanded intronic GAA repeat, results in mitochondrial iron accumulation, a decrease in mtDNA levels and severe deficiencies in the activities of complexes I–III, as well as aconitase. The function of frataxin is not known but it may be involved in FeS assembly as complexes I–III and aconitase are all FeS containing proteins. Such a function might also explain the deposition of iron in Friedreich's tissues. The OXPHOS defect and increased iron will probably result in increased oxidative stress and damage which in turn may cause the decrease in mtDNA levels as well as contribute to cell damage. The OXPHOS defect associated with paraplegin deficiency has only been defined at the histochemical level as a cytochrome oxidase defect. Further analysis will be required to determine the precise mitochondrial abnormalities in HSP. Wilson's disease is associated with liver failure or extrapyramidal dysfunction (including parkinsonism) and is due to mutations in the gene encoding a mitochondrial p-type ATPase [6]. Mitochondrial function has not been investigated in Wilson's disease but one would predict that accumulation of copper would

promote oxidative damage and result in an OXPHOS defect predominantly affecting complex IV (cytochrome oxidase).

Whilst FA, HSP and Wilson's disease may have OXPHOS deficiencies secondary to mutations in nuclear encoded mitochondrial proteins, HD involves respiratory chain defects that appear to be due to a non-mitochondrial protein – huntingtin. Huntingtin is a widely expressed protein of unknown function; an abnormal CAG expansion in the huntingtin gene produces the mutant protein with a polyglutamine stretch and causes HD. In HD, there is severe neuronal degeneration in the caudate, probably related to excitoxicity. Deficiencies of complexes II–IV and aconitase have been found in HD caudate [7–10]. It has been proposed that these defects arise as a result of mutant huntingtin expression, and nitric oxide, superoxide and peroxynitrite generation [10]. These mitochondrial abnormalities, although secondary, probably play an important role in the pathogenesis of HD. The role of any mitochondrial defect in AD is unclear. Whilst there is substantial evidence for deficiency of cytochrome oxidase in AD brain, its cause is unknown and might be related to oxidative damage or neuronal downregulation. An earlier report that the complex IV defect was due to mtDNA mutations [11] has subsequently been shown to be due to artefact [12]. Bonilla et al. review the possible role of mitochondrial dysfunction in AD in this issue.

The complex I deficiency in PD may be related to both primary and secondary factors. There is evidence that the complex I deficiency may be transferred with mtDNA from PD patients – particularly those with low complex I activity [13]. This implies that the defect is determined by a mtDNA abnormality – although does not discriminate between an inherited or somatic mutation. In a further proportion of PD patients, the complex I defect may be secondary or be enhanced by other factors, e.g. oxidative damage or dopamine.

There is evidence that both endogenously generated and exogenous toxins may impair OXPHOS function. Some, e.g. superoxide, nitric oxide, have been alluded to above, others, e.g. isoquinolines, may also be generated endogenously and inhibit respiratory complexes. The endogenous production of free radicals, secondary mtDNA damage and resulting impairment in OXPHOS may explain the mitochondrial changes that occur with aging. This area is reviewed in this issue by G.A. Cortopassi. Exogenous toxins that produce human disease have provided valuable clues to the possible role of mitochondrial dysfunction in the spontaneous disease counterpart. For instance, MPTP was found to inhibit complex I and induce parkinsonism in man and other primates. This stimulated the search for complex I deficiency in PD. 3-Nitropropionic acid induced a choreiform illness and death in a group of farm workers when accidentally consumed. This toxin and malonate are both potent complex II inhibitors and also induce caudate neuronal degeneration in animals – paralleling the biochemical and histological defect in HD brain.

Some causes of OXPHOS deficiency remain putative. For instance a defect of protein import would inevitably result in OXPHOS deficiency as so many components are nuclear encoded. However, it may be that such an abnormality would be incompatible with life. No doubt additional diseases will be characterised at the molecular level and found to involve mitochondrial proteins. This is a reflection not only of the large number of mitochondrial proteins synthesised, but also of the pivotal role of mitochondria in cellular metabolism.

References

[1] T. Bourgeron, P. Rustin, D. Chretien, M. Birch-Machin, M. Bourgeois, E. Viegas-Péquignot, A. Munnich, A. Rötig, Nature Genet. 11 (1995) 144–149.
[2] L. van den Heuvel, W. Ruitenbeek, R. Smeets, X. Gelman-Kohan, O. Elpeleg, J. Loeffen, F. Trijbels, E. Mariman, D. de Bruijn, J. Smeitink, Am. J. Hum. Genet. 62 (1998) 262–268.
[3] A.H.V. Schapira, J.M. Cooper, J.A. Morgan-Hughes, D.N. Landon, J.B. Clark, New Engl. J. Med. 323 (1990) 37–42.
[4] D.R. Dunbar, P.A. Moonie, H.T. Jacobs, I.J. Holt, Proc. Natl. Acad. Sci. USA 92 (1995) 6562–6566.
[5] H.C. Cock, S.J. Tabrizi, J.M. Cooper, A.H.V. Schapira, Ann. Neurol. 44 (1998) 187–193.
[6] S. Lutsenko, M.J. Cooper, Proc. Natl. Acad. Sci. USA 95 (1998) 6004–6009.
[7] V.M. Mann, J.M. Cooper, F. Javoy-Agid, Y. Agid, P. Jenner, A.H.V. Schapira, Lancet 336 (1990) 749.
[8] M. Gu, J.M. Cooper, M. Gash, V.M. Mann, F. Javoy-Agid, A.H.V. Schapira, Ann. Neurol. 39 (1996) 385–389.
[9] S.E. Browne, A.C. Bowling, U. MacGarvey, J. Baik, S.C.

Berger, M.K. Muqit, E.D. Bird, M.F. Beal, Ann. Neurol. 41 (1997) 646–653.
[10] S.J. Tabrizi, M. Cleeter, J. Xeureb, J.W. Taanman, J.M. Cooper, A.H.V. Schapira, Ann. Neurol. 45 (1999) in press.
[11] R.E. Davis, S. Miller, C. Hernstadt, S. Ghosh, E. Fahy, L.A. Shinobu, Proc. Natl. Acad. Sci. USA 94 (1997) 4526–4531.
[12] M. Hirano, A. Shtilbans, R. Mayeux, M.M. Davidson, S. DiMauro, J.A. Knowles, E.A. Schon, Proc. Natl. Acad. Sci. USA 94 (1997) 14894–14899.
[13] M. Gu, J.M. Cooper, J.W. Taanman, A.H.V. Schapira, Ann. Neurol. 44 (1998) 177–186.