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Mitochondrial Disorders: An Overview

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The past few years have seen extraordinary advances in our understanding of mitochondrial involvement in human pathology, and this has been reflected in the proliferation of reviews covering this topic. In this issue, which should prove complementary to others in this area, topics have been selected to cover regions of mitochondrial research in which there have been specific advances of considerable interest.

Mutations of mitochondrial DNA (mtDNA) are associated with a wide variety of clinical presentations and these are covered in the chapter by Schon *et al.* The ubiquity of mitochondria and the central role they play in cellular metabolism perhaps not surprisingly results in the potential for any tissue to dysfunction in the context of an inborn metabolic defect of the respiratory chain. Although mutations of mtDNA (deletions, duplications, point mutations) have been identified in a high proportion of patients, the role that these play in pathogenesis remains obscure. Indeed, the same mutations may be associated with very different phenotypes while, conversely, the same phenotype may be seen with different mutations. Standard explanations for these observations have involved random segregation of mutant mtDNA during embryogenesis, a threshold effect for biochemical expression, and differential dependence of tissues on oxidative phosphorylation for energy supply. However, it is certain that additional factors must be involved in pathogenesis. The mitochondrial respiratory chain is the source of >95% of superoxide ions in the aerobically respiring cell. Inhibition of the respiratory chain causes increased generation of free radicals, and the respiratory chain in turn may be inhibited by oxidative damage. This potential for a self-amplifying cycle of oxidative damage and respiratory chain dysfunction could contribute to the pathogenesis of mitochondrial disorders, particularly in vulnerable tissues such as the central nervous system. Schon *et al.* mention the potential role of autoimmunity in mitochondrial disorders; two reports have provided some support for this suggestion. The first involved the generation of a mitochondrial autoantibody in a boy with MELAS and the A3243G mutation, while the other reported the presence of circulating autoantibodies to optic nerve protein in patients with Leber's hereditary optic neuropathy (LHON) (Schapira *et al.*, 1990; Smith *et al.*, 1995).

The role of mtDNA mutations in the etiology and pathogenesis of LHON is covered in the article by Howell. Like the mitochondrial encephalomyopathies, LHON presents a fascinating challenge to our attempts to understand how specific mtDNA mutations, predominantly complex I gene point mutations in this case, may cause organ-specific (optic nerve) failure. The particular biochemical and anatomical features of the optic nerve may render it particularly susceptible to a respiratory chain deficiency. However, even the nature of the oxidative phosphorylation defect induced by these mutations seems variable, with some lack of direct linkage between ATP synthesis and complex I deficiency as assessed by enzyme assay. Although these "accidents of nature" may provide insight into, for instance, electron flow through the respiratory chain, they complicate our interpretation of the pathogenicity of LHON mtDNA mutations. The association of specific complex I mutations with LHON dystonia broadens the clinical spectrum of LHON and provides another intriguing link between archetypal mitochondrial diseases and movement disorders. This is particularly interesting in the light of the identification of complex I deficiency in some patients with idiopathic dystonia (Benecke *et al.*, 1992).

Nuclear control of respiratory chain expression is an important area not only in certain mitochondrial diseases, but also in our understanding of mitochondrial biogenesis and respiratory control. This area is

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covered by Scarpulla. Multiple sites exist as control points for nuclear factors in influencing mitochondrial biogenesis and biochemistry. Nuclear respiratory factors 1 and 2 have binding sites on *inter alia* genes for heme synthesis, mtDNA transcription and replication, and promoters for cytochrome oxidase genes. The control of oxidative phosphorylation genes appears to be linked into a system involving multiple cellular components and probably utilizes bidirectional flow of information between the nuclear and mitochondrial genomes.

Over 80% of the genes encoding subunits of the respiratory chain are located in the cell nucleus. Yet, to date, only one nuclear gene mutation causing a respiratory chain deficiency has been described (Bourgeron *et al.*, 1995). The contribution of nuclear genomic mutations to mitochondrial disease is covered in the articles by Taanman and Zeviani. Cytochrome oxidase (COX) deficiency most often occurs as part of a combined respiratory chain deficiency although specific mutations involving mtDNA COX genes have been described. The wealth of information already available on the structure of human COX is now being applied to the study of the molecular basis of COX deficiency. This is being aided by the use of monoclonal antibodies to mitochondrially and nuclearly encoded subunits of COX and by the use of complementation systems involving the use both of "control" rho zero (mtDNA-less) cell lines and those developed from patients. The former have been used to demonstrate nuclear involvement in mtDNA depletion syndrome, and the latter to show a common nuclear factor in a group of patients with Leigh's disease. Autosomal dominant mitochondrial myopathy has been linked to a locus on chromosome 10 in some families and to chromosome 3 in others. Additional families appear to have yet a different locus or loci, emphasizing the molecular heterogeneity of this disorder. The responsible genes have not been identified, although some candidate genes have been excluded.

It is now becoming clear that mitochondria play a pivotal role in the induction of apoptotic cell death. Zamzami *et al.* discuss how the collapse of the mitochondrial transmembrane potential and permeability transition lead to the release of pro-apoptotic proteins, one of which appears to be cytochrome *c*. These events precede nuclear DNA fragmentation. Opportunities already exist to manipulate mitochondrial permeability transition and this offers a novel means to regulate apoptotic cell death. Bcl-2 may inhibit apoptosis through its binding to the mitochondrial membrane adjacent to the permeability transition pore. Its ability to maintain the pore in a closed position will prevent the release of pro-apoptotic proteins. The role of mitochondria in both apoptotic and necrotic cell death may be relevant to several neurodegenerative diseases where there is evidence for respiratory chain dysfunction. This area is covered by Cooper and Schapira. Specific but different mitochondrial defects have been identified in Parkinson's disease substantia nigra, Huntington's disease caudate nucleus, and in Alzheimer's disease brain. In Parkinson's disease and Huntington's disease there are striking parallels between neurotoxin models of these diseases and the biochemical abnormalities in the postmortem brains studied. Whether the mitochondrial defects in these neurodegenerative diseases are the result of toxin exposure (exogenous or endogenous) is not yet clear. However, it is more likely that the mitochondrial deficiencies are the result of an interplay of primary and secondary factors. In this respect there is some evidence emerging that mtDNA plays a role in determining the complex I deficiency in Parkinson's disease.

Finally Taylor *et al.* discuss the possibilities for treatment of mitochondrial disease. This is a timely review as recent advances in cell biology are providing opportunities to manipulate the expression of mutant and wild type mitochondrial genomes. Standard therapies for mitochondrial disorders have, on the whole, proved disappointing. Genetic counselling remains an area of uncertain prediction. Genetic therapy for mtDNA mutations at present holds promise, and three strategies are considered in the review. The first involves the synthesis of mitochondrially encoded proteins on cytoribosomes and their import into mitochondria. The complexities of this approach, however, are likely to restrict its development to selective mutations. Complementation of mitochondrial gene expression has been successfully used in the import of a 322 base pair fragment into mammalian mitochondria. The third approach involves the use of sequence-specific inhibition of mutant mtDNA replication by oligonucleotides. Selective inhibition (by up to 80%) of the replication of mutant mtDNA bearing the "common" deletion and the A8344G $tRNA^{Lys}$ mutation without any effect on the wild type mtDNA has been demonstrated. As in all types

of gene therapy, delivery and maintenance of effect are problems which need to be overcome.

This series of reviews confirms that the intense activity in mitochondrial research continues to bear fruit and is providing us with information on basic mitochondrial biogenesis and biochemistry. The application of this information to human mitochondrial disease and its treatment will maintain the position of mitochondrial research at the forefront of advances in the biomedical sciences.

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