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RESEARCH NEWS

Answers to Missing mtDNA Found at Last

Review of Mandel H, Szargel R, Labay V *et al*. 2001 The deoxyguanosine kinase gene is mutated in individuals with depleted hepatocerebral mitochondrial DNA. Nat Genet 29:337–341 [Erratum: 2001 Nat Genet 29:491]; and Saada A, Shaag A, Mandel H *et al*. 2001 Mutant mitochondrial thymidine kinase in mitochondrial depletion myopathy. Nat Genet 29:342–344

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PRIMARY AND SECONDARY mitochondrial DNA depletion syndromes (MDS) (OMIM 251880) are characterized by a quantitative reduction in mitochondrial DNA (mtDNA) copy number (1). The structure, size, and sequence of the mtDNA are normal. Many genes have been investigated as candidates in primary MDS; none have been consistently shown to be associated with these conditions until the present papers. These articles (2, 3) report two genes – the gene for deoxyguanosine kinase (dGK) *DGUOK* in the hepatocerebral form, and the TK2 gene for mitochondrial thymidine kinase associated with myopathic form of MDS in some cases. This is a fascinating example of the defects in intergenomic communication, a defect in nuclear to mitochondrial DNA control. The mtDNA depletion is thus a distant effect of the primary enzyme deficiency. This has already lead in some cases to easier diagnostic tests in these conditions and to prenatal diagnostic possibilities, which were not previously possible.

The MDS are clinically heterogeneous disorders that may affect multiple or single organ systems, *e.g.* liver and/or muscle and brain, and/or heart and kidney. The hepatocerebral form can present with early infantile onset liver failure, jaundice, coagulopathy, hypoglycemia, lactic acidosis, and raised alpha-fetoprotein. Characteristic histopathologic features include cholestasis, fibrosis/cirrhosis, steatosis, and giant cell formation. These children may also have CNS neurodegenerative disease such as Leigh disease and/or muscular disease with ragged red fibers or cardiac involvement. Biochemical analyses of the affected tissues show nonspecific low activity of the mitochondrial respiratory chain complexes I, III, IV, and V which have mtDNA encoded subunits, relative to complex II, which is entirely nuclear encoded. Southern blot analysis shows a reduced mtDNA:nuclear DNA ratio (the deficient range is defined as less than 40% of mean control values) with patients often showing $<10\%$.

The importance of the nucleoside pools in mtDNA stability and maintenance were recognized with the discovery of the defects in thymidine phosphorylase in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) syndrome (4) and adenine nucleotide translocator ANT1 in adPEO (5). The cytosolic and mitochondrial nucleoside pools are balanced and essential even in non-replicating cells. There are no enzymes for nucleotide synthesis within the mitochondria - the pool thus depends on the salvage pathway. Imbalance in these pools has been associated with increased DNA damage. There are four human deoxynucleoside kinases: TK1, TK2, dGK, and deoxycytidine kinase (dCK). DGK and TK2 are essential enzymes in the intramitochondrial nucleotide salvage pathway, which is the sole source of nucleosides for mtDNA synthesis when cytosolic dNTP synthesis is down regulated in non-replicating cells. DGK phosphorylates deoxyadenine and deoxyguanosine to the deoxynucleotide monophosphates. TK2 phosphorylates deoxythymidine, deoxycytidine, and deoxyuridine. Mutations in *DGUOK* will thus result in an imbalance in the nucleotide pool and impaired mtDNA synthesis.

Employing a genome-wide screen using homozygosity mapping strategy the authors (2) identified linkage to the *DGUOK* gene on chromosome 2p13 and a single base deletion segregating with the hepatocerebral form of MDS. Saada *et al*. (3) described four families with children affected with muscular MDS and identify mutations in the *TK2* gene on chromosome 16q22. They also describe the reduced activity of TK2 with deoxythymidine in the affected muscle tissue mitochondria. Patients with depletion also have compensatory increase in activity of the other nonmutated deoxynucleoside kinases (3). More recently duplications, deletions, and other missense point mutations have been described in *DGUOK* and there is some preliminary evidence for possible genotype/phenotype correlation (6).

Possible explanations for the differing expression of these autosomally inherited biochemical defects in different patients and tissues have been discussed. For *DGUOK*, possibilities include the differing expression of deoxycytidine kinase (dCK) expression, which, with overlapping phosphorylation function, could compensate for a defect in dGK. However, dCK has very low expression in the high energy requiring organs, brain, and liver. TK2 activity in muscle is low compared to other tissues so these tissues, which are non-replicating and therefore do not have active thymidine kinase I, may be more at risk of ex-

pressing disease. There may also be modifying effects of the deoxynucleotide carrier/s, which transport cytosolic deoxynucleotides into the mitochondrion across the impermeable inner mitochondrial membrane. All these possibilities need to be further investigated for us to have a better understanding of the pathogenesis of these conditions. In addition, not all patients with hepatic or muscular mtDNA depletion have been found to have mutations in *DGUOK* or TK2 indicating that other gene defects, perhaps the other nucleotide kinases, are involved in MDS and need further study.

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