CRISIS IN ENERGY METABOLISM

MITOCHONDRIAL DEFECTS AND A NEW DISEASE ENTITY

Akademisk avhandling

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Avhandlingen baseras på följande delarbeten:

I. A-R. Moslemi, C. Lindberg, J. Toft, E. Holme, **G. Kollberg**, A. Oldfors. A novel mutation in the mitochondrial $tRNA^{Phe}$ gene associated with mitochondrial myopathy. *Neuromuscular disorders* 2004;14:46-50

II. **G. Kollberg**, A-R. Moslemi, C. Lindberg, E. Holme, A. Oldfors. Mitochondrial myopathy and rhabdomyolysis associated with a novel nonsense mutation in the gene encoding Cytochrome *c* Oxidase subunit I. *Journal of Neuropathology and Experimental Neurology* 2005; 64:123-128

III. **G. Kollberg**, M. Jansson, Å. Pérez-Bercoff, A. Melberg, C. Lindberg, E. Holme, A-R. Moslemi, A. Oldfors. Low frequency of mtDNA point mutations in patients with PEO associated with *POLG1* mutations. *European Journal of Human Genetics* 2005;13:463-469

IV. **G. Kollberg**, A-R. Moslemi, N. Darin, I. Nennesmo, I. Bjarnadottir, P. Uvebrant, E. Holme, A. Melberg, M. Tulinius, A. Oldfors. *POLG1* mutations associated with progressive encephalopathy in childhood. *Journal of Neuropathology and experimental Neurology* 2006;65:758-768

V. **G. Kollberg**, M. Tulinius, T. Gilljam, I. Östman-Smith, G. Forsander, P. Jotorp, A. Oldfors, E. Holme. Muscle Glycogen Storage Disease 0 – A Cause of Sudden Cardiac Death. *Submitted*

ABSTRACT

CRISIS IN ENERGY METABOLISM

MITOCHONDRIAL DEFECTS AND A NEW DISEASE ENTITY

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Impairment of energy metabolism may be associated with severe implications for affected individuals since all fundamental cell functions are energy-dependent. Disorders of energy metabolism are often genetic and associated with defects in the oxidative phosphorylation in mitochondria. This thesis addresses the pathogenesis in some mitochondrial disorders and a new disease entity associated with defects in the glycogen metabolism.

In paper I we report on a primary mutation in mitochondrial DNA. We identified a T C mutation at position 582 in the gene for $tRNA^{Phe}$ in a case of mitochondrial myopathy. The mutation alters a conserved base pairing in the aminoacyl stem of the tRNA. By analysis of single muscle fibers we showed that the level of heteroplasmy (proportion of mutant mtDNA) was higher in muscle fibers with defective cytochrome *c* oxidase (COX) activity compared to normal muscle fibers. Based on these findings we conclude that this mutation was responsible for the disease.

In paper II we investigated a 30-year-old woman, who presented with an attack of acute rhabdomyolysis. We found an isolated deficiency of COX and a novel nonsense mutation in mtDNA in the gene encoding COX subunit I. In addition to its catalytic function, our data clearly indicates an important function of subunit I for the assembly of COX. The mutation was restricted to the patient's muscle, but was not detectable in myoblasts, cultured from satellite cells isolated from affected muscle tissue. This result may have interesting implications for the natural evolution of the disease and perhaps therapy, since regenerating muscle occurs by proliferation of satellite cells.

In paper III we investigated patients with mitochondrial diseases (progressive external ophthalmoplegia, PEO) due to primary mutations in *POLG1* encoding mtDNA polymerase gamma (Pol) and secondary multiple mtDNA deletions. The results show that it is very unlikely that mtDNA point mutations contribute to the pathogenesis in PEO patients with primary *POLG1* mutations, and that the mechanism by which mutant Pol cause mtDNA deletions does not involve mtDNA point mutations as an intermediate step, as has been previously proposed.

In paper IV mtDNA alterations and pathology of muscle, brain and liver was investigated in children with Alpers-Huttenlocher syndrome (AHS), a fatal neurodegenerative disease associated with liver failure. All children had compound heterozygous missense mutations in *POLG1*. We provide evidence that AHS is a mitochondrial disease by demonstrating mtDNA alterations (reduced mtDNA copy number and multiple mtDNA deletions). Liver disease was triggered by valproate treatment in several cases possibly due to severe respiratory chain deficiency, which was demonstrated in liver tissue in one case.

In paper V we report on a new disease entity "Muscle glycogen storage disease type zero" due to a homozygous stop mutation in the muscle glycogen synthase gene (*GYS1*). We performed investigations on a family where one child suffered sudden cardiac death at the age of 10 and his younger brother showed muscle fatigability and hypertrophic cardiomyopathy. In muscle there was a profound glycogen deficiency and an almost total predominance of oxidative muscle fibers.

Keywords: Energy metabolism, mitochondrial disorders, point mutation, mtDNA, multiple mtDNA deletions, Alpers-Huttenlocher syndrome, *POLG1*, Polymerase gamma, *GYS1*, glycogen synthase

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