Keynote Address
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A MITOCHONDRIAL ETIOLOGY OF COMPLEX DISEASES

In spite of prodigious efforts to identify nuclear DNA (nDNA) genetic variants associated with complex diseases, the pathophysiology of these disorders remains unclear. Since the brain is 2% of the body weight yet uses 20% of the oxygen, it follows that subtle reductions in mitochondrial oxidative phosphorylation (OXPHOS) should have marked effects on the brain. Similarly, the heart, muscle, renal and endocrine systems also have high energy demands. The mitochondria produce much of the energy used by our tissues and the mitochondrion is assembled from between one to two thousand nDNA coded genes plus 37 mitochondrial DNA (mtDNA) coded genes which include 13 of the most important OXPHOS coded genes plus the tRNAs and rRNAs for their expression. The mtDNA is maternally inherited, present in thousands of copies per cell, and can encompass different percentages of mutant and normal mtDNAs (heteroplasmy) generating variable OXPHOS defects and clinical phenotypes. As the proportion of mutant mtDNA heteroplasmy increases, bioenergetic function declines, and the mitochondria signal to the nucleus-cytosol the changing energetic state through mitochondrially-generated high energy intermediates (ATP, acetyl-CoA, S- adenosylmethionine, α-ketoglutarate, etc.). This induces changes in the epigenome which precipitate phase changes in gene expression, produce discrete bioenergeic states and cellular and clinical phenotypes including metabolic and neuromuscular disorders. There are three clinically relevant classes of mtDNA variants: ancient mtDNA lineages (haplogroups), recent deleterious mutations, and somatic mutations. Case control studies have identified mtDNA haplogroup lineages associated with predisposition to a variety of complex diseases. Maternally inherited deleterious mtDNA mutations have been linked to a variety of metabolic and degenerative diseases. Somatic mtDNA mutation levels are elevated in neurological, cardiac and muscle disorders. Proof that mitochondrial defects are sufficient to cause common diseases comes from the generation of mice which harbor mutations in both nDNA and mtDNA coded genes which then manifest neurological, cardiac, and metabolic diseases. Creation of a mouse harboring the human pathogenic mtDNA *ND6* P25L mutation resulted in neurodegenerative diseases. Mice harboring a mtDNA *COI* mutation manifest cardiomyopathy, myopathy, and metabolic disease. Simply mixing two different normal mtDNAs within the mouse female germline resulted in reduced activity, hyper-excitability, and a severe learning defect. In humans, mutations in the brain-heart-muscle isoform of the adenine nucleotide translocator (*ANT1*) results in autosomal recessive cardiomyopathy and myopathy, the severity of which is determined by the background mtDNA haplogroup. Inactivation of the mouse *Ant1* gene also results in myopathy and cardiomyopathy and combination of *Ant1*-deficiency with the mtDNA *ND6* mutation greatly increases the severity of the cardiomyopathy. Analysis of the fetal *Ant1*-deficient mouse brain has revealed that cortical interneuron migration but not pyramidal neuron migration is impaired. This could generate cortical excitation-inhibition imbalance which has been hypothesized to cause a range of human hyper-excitation syndromes (ADHD, autism, schizophrenia). Mice harboring various nDNA and mtDNA gene mutations and exposed to acute stress manifest marked differences in the hypothalamic-pituitary-adrenal (HPA) and sympathetic adrenal-medullary (SAM) axis, catecholamine levels, metabolites, and inflammatory cytokines. Hence, individual differences in mitochondrial function may be central to differential human sensitivity to a wide range of common clinical problems from cardiomyopathy to metabolic syndrome and from neurodegeneration to psychiatric disorders.