

with degenerative encephalopathy, and indicated alteration of F₁ biosynthesis [1]. The search in other cases for disease causing gene by expression profiling and homozygosity mapping, identified mutation in *TMEM70* gene encoding a 30 kDa mitochondrial protein of unknown function [2]. Enzyme defect was complemented by *wtTMEM70* and *TMEM70* protein turned out to be a novel ancillary factor of ATP synthase biosynthesis, interestingly the first one specific for higher eukaryotes. Homozygous *TMEM70* c.317-2A>G mutation leading to aberrant splicing and loss of the *TMEM70* mRNA was found in 24 patients, one patient was compound heterozygote for c.118_119insGT frame-shift mutation. Since then *TMEM70* mutations were found in other patients [3] thus being the most frequent cause of ATP synthase deficiency. Nevertheless, other cases may exist where additional nuclear genes are involved.

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4L.4 Mitochondrial pathways to autism

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Autism is a severe pervasive developmental disorder characterized by variable degrees of impairment in language, communication and social skills, as well as by repetitive and stereotypic patterns of behaviour. Despite strong familial components, clinical and genetic complexities have posed a major challenge to our understanding of autism pathogenesis. A significant subset of autistic patients display biochemical or neuropathological evidence of mitochondrial dysfunction and/or oxidative stress. However, only in a very few cases abnormal energy metabolism could be linked to a specific genetic defect. Interest in assessing the role of mitochondria in this disorder has been revitalized by the association between autism and variants of the *SLC25A12* gene [1], which encodes the predominant isoform of the mitochondrial aspartate/glutamate carrier (AGC) in brain [2]. Cytosolic Ca²⁺ can rapidly activate AGC transport through four "EF-hand" domains located at its N-terminus, thereby increasing the NADH/NAD ratio in the mitochondrial matrix and consequently boosting electron flow through the respiratory chain and ATP generation by oxidative phosphorylation [3]. Post-mortem studies of temporocortical gray matter from matched patient-control pairs revealed that AGC transport rates were significantly higher in brains from autistic patients [4]. This difference was blunted by Ca²⁺ chelator EGTA and direct fluorimetric measurements confirmed significantly higher Ca²⁺ levels in the patients, compared to their matched controls [4]. Oxidized mitochondrial proteins were markedly increased in the majority of the patients tested. Interestingly, oxidative damage correlated with the reduction of complex I activity indicating that excessive Ca²⁺ levels boost AGC activity in neurons and, to a more variable degree, cause oxidative stress and mitochondrial dysfunction in autistic brains. Furthermore, we identified a protective *SLC25A12* gene variant in a sizable group of unaffected siblings modulating AGC1 mRNA levels and protein activity. Our results suggest that mitochondria may play a critical role in the cascade of signalling events leading to autism and in determining to what extent different prenatal triggers will derange neurodevelopment and yield abnormal postnatal behaviour.

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4L.5 Mitochondrial energy, redox dysregulation in human heart failure: Role of post-oxidative enzyme modification

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Heart failure is characterized by chronic, progressively worsening, insufficient energy supply and failure of ventricular contraction for the maintenance of blood circulation. We examined the abundance and activity of crucial mitochondrial enzymes as potential contributors to heart failure. Human left ventricular tissue was biopsied from non-failing donor hearts and end-stage failing hearts. Activity of complexes I and IV, the NADH-linked Krebs enzymes isocitrate dehydrogenase and malate dehydrogenase, NADPH transhydrogenase and aconitase was lower in failing hearts, as determined spectrophotometrically, while that of complexes II, III and citrate synthase was unchanged. Specific protein expression of each of these, determined by western blotting did not differ between the non-failing and failing heart groups, implying post-translational protein perturbation. Oxidative modification was explored as an underlying cause of enzyme dysfunction. Of the three oxidative markers measured, total mitochondrial protein carbonylation was greater by 31% in the failing tissues, while levels of 4-hydroxy-2-nonenal and protein nitration did not differ. Isolation of complexes I, IV and V by immunocapture revealed that subunits containing the iron-sulphur or heme redox centers were targets of oxidative modification, which may explain decreased activity in these enzymes. Notably the lower level of mitochondrial activity in heart failure coincided with significantly higher levels of oxidized glutathione, lower glutathione reductase activity, and lower content of total Coenzyme Q₁₀, cardiolipin, total adenine nucleotides, NADH and NADPH. In conclusion, the energy insufficiency of the failing human heart involves impaired activity of key mitochondrial enzyme subunits, at least in part due to oxidative modification. Thus the management of reactive oxygen species which markedly deteriorates concomitant with augmenting contractile failure may be a critical factor contributing to spiralling energy deficiency in the failing human heart.

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4L.6 Oxygen tension significantly affects mitochondrial mass and structure in human fibroblasts

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Oxygen homeostasis is essential for normal cellular function; as oxygen level decreases (hypoxia), cells respond by changing their metabolism and by activating hypoxia-inducible factor dependent gene transcription to adapt and survive. Mitochondria sense the