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MITOCHONDRIAL DYNAMICS AND OXPHOS (PATHO)PHYSIOLOGY - Normal cell functioning and survival requires energy in the form of ATP that is generated by a variety of metabolic pathways. Within this metabolism, the mitochondrial oxidative phosphorylation (OXPHOS) system is among the prime producers of ATP. Proper OXPHOS function is also required to sustain many other mitochondrial processes including the exchange of ions and metabolites with the cytosol. In this sense, the OXPHOS system plays a key role in various cellular processes like adaptive thermogenesis, innate immune responses, calcium and redox signalling, and programmed cell death (apoptosis). The OXPHOS system consists of 5 multi-subunit complexes (CI to CV) that contain 92 different structural proteins encoded by the nuclear (nDNA) and mitochondrial DNA (mtDNA). Biogenesis of a functional OXPHOS system further requires the assistance of nDNA-encoded OXPHOS assembly factors (chaperones), of which 35 are currently identified. OXPHOS and mitochondrial dysfunction are not only associated with relatively rare monogenic mitochondrial disorders but also observed during more common pathologic conditions, such as Alzheimer's, Huntington's and Parkinson's disease, cancer, cardiac disease, diabetes, epilepsy, and obesity. In addition, a progressive decline in the expression of mitochondrial genes is observed during normal human aging and mitochondrial function is inhibited by environmental toxins and frequently used drugs. Mutations in OXPHOS structural genes are associated with neurodegenerative diseases including Leigh Syndrome, which is probably the most classical OXPHOS disease during early childhood. My research focuses on gaining a quantitative mechanistic understanding of mitochondrial (patho)physiology at the (sub)cellular level in OXPHOS disorders. To this end, the following research questions are addressed: (**i**) How are mitochondrial (ultra)structure and metabolic (dys)function connected? (**ii**) How does mitochondrial (dys)function affect cellular (dys)function? (**iii**) How do cells adapt to mitochondrial dysfunction? (**iv**) How can mitochondrial dysfunction be mitigated?Given the tight integration of mitochondrial and cellular metabolism, the above questions are addressed in living cell systems. To this end, protein-based and chemical fluorescent reporter molecules are introduced in healthy and patient-derived primary cells, as well as established cell lines to allow analysis of mechanistic aspects. (Patho)physiology is then investigated using biochemical and molecular cloning techniques, high-resolution respirometry, state-of-the-art quantitative (sub)cellular life cell microscopy, single-molecule spectroscopy, mathematical modelling, image processing, data mining and machine learning techniques.

Key publications

- Eisenberg et al. (**2008**) *Hum. Mol. Genet.* 17, 3663-3674.
- Distelmaier et al. (**2009**) *Brain* 132:833-842.
- Koopman et al. (**2010**) *Antioxidants and redox signaling* 12:1431-1470.
- Dieteren et al. (**2011**) *Proc. Natl. Acad. Sci. USA* 108:8657-8662.
- Distelmaier et al. (**2012**) *Antioxidants and redox signaling* 17:1657-1669.
- Koopman et al. (**2012**) *N. Eng. J. Med.* 366:1132-1141.
- Koopman et al. (**2013**)*EMBO J.* 32:9-29.
- Willems et al. (**2013**) *Antioxidants and redox signaling therapeutics* 18:129-138.