

Mitochondrial dysfunction in neurodegenerative diseases, inherited metabolic disorders and in the aging process

Mitochondria supply the majority of cellular ATP by the process of oxidative phosphorylation and are hence a key player in cellular homeostasis. It is therefore not surprising that mitochondrial dysfunction can be detrimental to cell viability causing tissue malfunction and severe pathological disorders. Most of the known mitochondrial disorders ultimately result in an impaired ATP synthesis. Hence, high energy demand of tissues like skeletal muscle, liver, heart, and brain are most severely affected by the bioenergetic crisis. Typical clinical manifestations of mitochondrial disorders are myopathy, seizures, encephalopathy and cardiomyopathy.

We are interested in how mitochondrial dysfunction results in pathology in different groups of diseases and how this effect can be modulated. Inherited mitochondrial disorders can be caused by genetic alterations of the nuclear or mitochondrial genome. Epidemiological studies suggest that the occurrence of such a mitochondrial disease may be as high as 1:5,000 making it the most commonly inherited neurological disorder. Besides mitochondrial disease, mitochondrial dysfunction is also associated with neurodegenerative diseases (e.g. Parkinson's disease, Alzheimer's disease), metabolic disorders (obesity, Type 2 Diabetes) and the aging process, but the role of mitochondria in the onset and progression of these disorders is still unclear.

We are particularly interested in the following questions:

- What are the cellular responses to the mitochondrial dysfunction and how do these responses contribute to the pathology?
- How can the mitochondrial dysfunction and its effects be prevented or reversed in different diseases?
- Does a maintained mitochondrial function prevent the onset and/or progression of neurodegenerative or age-associated diseases?

To answer these questions, we are generating mouse models with systemic or tissue-specific mitochondrial dysfunction. Along with already existing murine lines, we will characterize the newly established mouse strains on the phenotypical, physiological and biochemical level. These studies will be complemented by analysis of cell lines from patients with diagnosed mitochondrial disease. We will further assess the efficacy of different strategies to circumvent or prevent the mitochondrial dysfunction both *in vitro* and *in vivo*.

Publications

- 1: Wenz T, Rossi SG, Rotundo RL, Spiegelman BM, Moraes CT (2009) Increased muscle PGC-1alpha expression protects from sarcopenia and metabolic disease during aging. *Proc Natl Acad Sci U S A* **106**:20405-10.
- 2: Wenz T (2009) PGC-1alpha activation as a therapeutic approach in mitochondrial disease. *IUBMB Life* **61**:1051-62.
- 3: Wenz T, Luca C, Torraco A, Moraes CT (2009) mTERF2 regulates oxidative phosphorylation by modulating mtDNA transcription. *Cell Metab.* **9**:499-511.
- 4: Wenz T, Diaz F, Hernandez D, Moraes CT (2009) Endurance exercise is protective for mice with mitochondrial myopathy. *J Appl Physiol.* **106**:1712-9.
- 5: Wenz T, Diaz F, Spiegelman BM, Moraes CT (2008) Activation of the PPAR/PGC-1alpha pathway prevents a bioenergetic deficit and effectively improves a mitochondrial myopathy phenotype. *Cell Metab.* **8**:249-56.