Aim 3: Quality control of mitochondria in neurodegenerative diseases
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It has been proposed that mitochondrial defects may be a key determinant in neurodegenerative diseases, leading to energy depletion and reactive oxygen species overload. In such condition, the mitochondrial quality control system allows to restore normal functioning of mitochondria, by both reducing damaged mitochondrial components or by degrading the entire organelle through specific autophagy, so called mitophagy. In the last few years, we have analyzed the role of mitochondrial quality control in Huntington's disease (HD). We demonstrated that the removal of defective mitochondria is impaired in striatal cells expressing HD mutation. In contrast overexpressing PTEN-induced putative kinase 1 (PINK1), that controls mitophagy, partially restores the degradation of non-functional mitochondria in these cells. We also provided *in vivo* evidence of a beneficial effect of PINK1. While expression of mutant Huntingtin in *Drosophila* neurons leads to mitochondrial fragmentation and accumulation of abnormal shaped mitochondria, PINK1 ameliorates mitochondrial morphology. Interestingly, PINK1 rescues ATP levels, neuronal integrity and adult fly survival. Altogether, our findings suggest that mitophagy is altered in the presence of mutant Huntingtin and that increasing PINK1/Parkin mitochondrial quality control pathway may improve mitochondrial integrity and neuroprotection in HD.

We recently investigated the role of mitochondrial quality control in another neurodegenerative disease: the amyotrophic lateral sclerosis (ALS). Among the recent ALS-linked genes, mutations in TAR DNA-binding protein 43 kDa (TDP-43) are not only associated to familial ALS but also cytoplasmic accumulation of wild-type TDP-43 is found in almost all patients with sporadic ALS. We thus set up an analysis on flies expressing human wild-type or mutant TDP-43. We showed that expression of TDP43 in *Drosophila* neurons also leads to mitochondrial fragmentation. This is correlated by a reduced expression of the profusion protein Mitofusin. TDP-43, which regulates mRNA metabolism, seems to directly target *mitofusin* transcript. More importantly, we provided the first *in vivo* evidence that increasing Mitofusin expression mitigates TDP-43-induced defects at the neuromuscular junction as well as ameliorates locomotor behavior. Taken together, our data prompt us to propose that the beneficial effects of Mitofusin result from a better functioning of mitochondria. At present, we want to further dissect the mechanisms.

We are pursuing our investigations to identify novel targets in order to maintain mitochondrial homeostasis or functioning. In particular we are studying interactions between endoplasmic reticulum and mitochondria. Endoplasmic reticulum-mitochondria interplay influences activities of numerous mitochondrial enzymes including pyruvate dehydrogenase, enzymes catalysing Krebs cycle and even oxidative phosphorylation.