LIVE IMAGING OF MITOCHONDRIAL DYNAMICS IN AMYOTROPHIC LATERAL SCLEROSIS

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Introduction: Mitochondria have gained popularity in the field of neurodegenerative diseases. This is not surprising considering the fundamental functions of mitochondria in intracellular Ca$^{2+}$ homeostasis and ATP synthesis. Remarkably, many diseases of mitochondria dysfunction result in neurodegeneration.

Aims: Although mitochondrial defects appear early during disease pathogenesis and axonal transport abnormalities have been suggested, there is little evidence of abnormal mitochondrial dynamics in amyotrophic lateral sclerosis (ALS).

Methods: Our research explores mitochondrial transport and dynamics using a photo-activatable, fluorescent protein targeted to mitochondria (mitoDendra), and live imaging microscopy, both on isolated neurons and on the whole mice.

Results: Motor neurons (MN) from mutant SOD1 (G93A) have smaller mitochondria, and reduced density/mass, as compared to WT SOD1 and non-transgenic controls. Interestingly, size abnormalities are confined to the distal segments of axons. Mitochondria in mutant MN have reduced motility (mostly affecting retrograde transport) and less frequent fusion. We estimated mitochondrial membrane potential ($\Delta\Psi$) and demonstrated that mobile (anterogradely moving) mutant mitochondria have significantly lower $\Delta\Psi$, which resulted in an overall reduction of $\Delta\Psi$ in distal segments of mutant SOD1 MN. We also observed fewer and smaller synaptic puncta; synaptic loss correlated with lack of mitochondria at synapses in mutant SOD1 MN.

Conclusions: A better understanding of the changes in the dynamics of mitochondria in ALS will contribute to understand their role in disease progression. Furthermore, the imaging protocols and techniques that we are developing to study mitochondrial transport defects will be applicable not only to ALS, but also to many other neurodegenerative disorders.