Peter Hollenbeck 2

**Mitochondrial Transport, Metabolism and ROS Production in Disease Models**

Mitochondrial dysfunction has been implicated in a variety of neurodegnerative diseases, and the major effect of this dysfunction is usually posited to be ROS damage to the cell. The reasoning behind this has been that defects in components of the electron transport chain (ETC) will result in the excessive production of ROS at complexes I and III. However, it is difficult from first principles to determine whether a given malfunction or mutation in the ETC will cause the generation of ROS to increase, decrease, or remain the same. In addition, more recent and accurate estimates of the amount of ROS produced by the ETC are much lower than classical figures – which are still often cited. Thus, we suggest that individual mitochondrial disorders must be evaluated at the cell and tissue level in order to determine the true nature of their cellular neuropathology. We have used the Drosphila larva as a model system in which to analyze mitochondrial axonal transport, distribution, membrane potential and ROS production in an intact nervous system. We first investigated Friedreich ataxia, a neurodegenerative disorder resulting from frataxin deficiency, that has been suggested to involve progressive cellular damage from oxidative stress. We used Drosophila larvae with reduced frataxin expression (DfhIR) to evaluate various measures of function from the cell bodies to the synapses, and throughout development. We found that although dying-back neuropathy in DfhIR larvae did not occur until late 3rd instar, reduced membrane potential was already apparent at 2nd instar throughout the motor neurons. The defects in axonal transport of mitochondria were counterintuitive: although we expected a failure to deliver mitochondria to DfhIR synapses, instead we found reductions in retrograde mitochondrial traffic late in development such that synapses accumulated a higher density of mitochondria – but these were largely depolarized. Notably, increased ROS production was not detected in any neuronal region or developmental stage in DfhIR larvae. We have proposed that pathology in the frataxin-deficient nervous system involves decreased membrane potential and ATP production followed by failures of mitochondrial transport and NMJ function. We are currently evaluating Parkinson’s disease-related mutants to understand their particular cellular neuropathologies.

**Suggested readings:**

Puccio H, Koenig M (2002) Friedreich ataxia: a paradigm for mitochondrial diseases. *Curr Opin Genet Dev* 12:272-277.

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