A Drosophila model for Duchenne Muscular Dystrophy

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Duchenne muscular dystrophy (DMD) is an X-linked disease occurring in ~1:3000 boys. Symptoms include severe muscle wasting and mild mental retardation. A lack of the dystrophin protein causes the disease. Dystrophin is part of a large complex of proteins known as the dystrophin glycoprotein complex. This complex is purported to have several roles, e.g., structural support, signaling and serving as a scaffold for acetylcholine receptors at the mammalian neuromuscular junction. The mechanisms underlying the onset and progression of DMD are still largely unknown.

We are using *Drosophila melanogaster* as a model system to explore the dystrophin function in the nervous system and musculature. *Drosophila* has an advantage over the mammalian models of DMD, i.e., the dystrophin knockout mouse, in that usually only a single member of each of the major DGC protein classes is encoded in the fly genome. The compact and segmentally-reiterated morphology of the fruitfly also greatly facilitates phenotypic characterization. Furthermore, a number of research tools are available, e.g., markers to follow the trajectories of individual neurons, live cell imaging using GFP transgenes, standard behavioral assays and electrophysiology. Finally, the powerful genetic approaches possible in Drosophila can be used to identify genes that interact with the disease-related gene. Increasingly, therefore, Drosophila is being used as a model for human disease, including neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's disease.

We have generated Drosophila mutants, which lack one or more of the dystrophin isoforms. Mutant flies show clear differences from controls in behavioural assays.These mutants also show defects in the development of the musculature, wing veins and neuromuscular junction. Electrophysiological analysis of mutant larval neuromuscular junctions is underway and will be discussed.

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