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Human Sporadic Inclusion Body Myositis in a *Drosophila melanogaster* Model System

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Project advisor: Craig Woodard

Sporadic Inclusion Body Myositis (s-IBM) is an inflammatory muscular disease characterized by slow weakening of proximal and distal muscles. Muscles affected by s-IBM can be distinguished by autoimmune inflammatory features, with degenerative features including accumulation of amyloid-related proteins. Amyloid precursor protein (APP) is a type I transmembrane glycoprotein that can be cleaved into Aβ peptides by β-secretases (BACE), and γ-secreatases. It is hypothesized that the intracellular accumulation of Aβ peptides in the s-IBM muscle cells is closely related to the abnormal cleavage by BACE. It has been also suggested that under some physiological and pathological conditions, human APP (hAPP) can destruct mitochondria causing transmembrane arrest by preventing cytochrome c oxidase subunits IV and Vb from entering the mitochondria[1].

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In this project, *Drosophila melanogaster* is used as a model to study human s-IBM. It has been confirmed that in *Drosophila*, the targeted expression of APP and BACE led to formation of β-amyloid aggregates, age-dependent neurodegeneration, and shortened life-span[2]. Based on the previous work suggesting an involvement of BACE with hAPP[3], transgenic flies expressing either hAPP or BACE alone, expressing both hAPP and BACE, and wild type flies were studied for their dorsal thoracic muscle using Transmission Electron Microscopy. Comparing the morphology of the myofibrils and mitochondria of these flies revealed more severe mitochondrial defects in the hAPP-, BACE-, and both hAPP and BACE-expressing flies than in the wild type. However, there was no visible abnormality found in the myofibril itself for any of the genotypes. Although preliminary, the difference in the level of swollen or destructed mitochondria in BACE or hAPP expressing flies compared to the wild type flies suggests some involvement of these molecules in muscle degeneration. More detailed and quantitative study of the mitochondria and muscle structure would help clarify the relationship between BACE and s-IBM.

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[1] Anandatheerthavarada H.K., Biswas G., robin M.A., and Avadhani N.G. 2003. Mitochondrial targeting and a novel transmembrane arrest of Alzheimer's amyloid precursor protein impairs mitochondrial function in neuronal cells. *J Cell Biol.* 161:41-54.
[2] Greeve I., Kretzschmar D., Tschape J.A., Beyn A., Brellinger C., Schweizer M., Nitsch R.M., and Reifegerste R. 2004. Age-dependent neurodegeneration and Alzheimer-amyloid plaque formation in transgenic Drosophila. *J Neurosci.* 24(16):3899-906.
[3] Nitta, M. 2007. A *Drosophila melanogaster* model for Human Inclusion Body Myositis. [BA thesis]. South Hadley (MA): Mount Holyoke College.

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