Scott Brady 3

**Adult-Onset Neurodegeneration as Dysferopathies**

**Abstract**

Many adult-onset neurodegenerative diseases develop as dying back neuropathies, including Alzheimer’s, Huntington’s and Parkinson’s disease. This pattern of neurodegeneration can result from changes in fast axonal transport (FAT) and the evidence is mounting that pathogenic changes in FAT are a pathogenic hallmark in each of these diseases. The molecular basis underlying the observed inhibition of FAT is now beginning to emerge. For example, selective reductions in FAT are seen in polyglutamine-expansion diseases such as Huntington’s disease as well as in Alzheimer’s disease can be related to specific kinase pathways and specific toxic motifs. Inhibition of FAT is associated with changes in neuronal kinases and phosphorylation of molecular motor proteins like kinesin and dynein. Pharmacological and biochemical studies in models of different neurodegenerative diseases show that inhibition of FAT is a consequence of dysregulation of specific signaling pathways, that lead to the characteristic phenotype of each disease. The common pathogenic features of these diseases indicate that they represent a distinctive class of neuropathology which we have termed “dysferopathy” from the Greek word “fero” meaning to transport or carry.

**Readings**:

1. Morfini GA, Burns M, Binder LI, Kanaan NM, LaPointe N, Bosco DA, Brown RH, Jr., Brown H, Tiwari A, Hayward L, Edgar J, Nave KA, Garberrn J, Atagi Y, Song Y, Pigino G, Brady ST. Axonal transport defects in neurodegenerative diseases. J Neurosci. 2009;29(41):12776-86. PMCID: 2739046.

1. Pigino G, Morfini G, Atagi Y, Deshpande A, Yu C, Jungbauer L, LaDu M, Busciglio J, Brady S. Disruption of fast axonal transport is a pathogenic mechanism for intraneuronal amyloid beta. Proc Natl Acad Sci U S A. 2009;106(14):5907-12. PMCID: 2667037.

1. Morfini GA, You YM, Pollema SL, Kaminska A, Liu K, Yoshioka K, Bjorkblom B, Coffey ET, Bagnato C, Han D, Huang CF, Banker G, Pigino G, Brady ST. Pathogenic huntingtin inhibits fast axonal transport by activating JNK3 and phosphorylating kinesin. Nat Neurosci. 2009;12(7):864-71. PMCID: 2739046.

1. Pigino G, Morfini G, Atagi Y, Deshpande A, Yu C, Jungbauer L, LaDu M, Busciglio J, Brady S. Disruption of fast axonal transport is a pathogenic mechanism for intraneuronal amyloid beta. Proc Natl Acad Sci U S A. 2009;106(14):5907-12. PMCID: 2667037.

1. Bosco DA, Morfini G, Karabacak NM, Song Y, Gros-Louis F, Pasinelli P, Goolsby H, Fontaine BA, Lemay N, McKenna-Yasek D, Frosch MP, Agar JN, Julien JP, Brady ST, Brown RH, Jr. Wild-type and mutant SOD1 share an aberrant conformation and a common pathogenic pathway in ALS. Nat Neurosci. 2010;13(11):1396-403. PMCID: 2967729.

1. Kanaan NM, Morfini GA, Lapointe NE, Pigino GF, Patterson KR, Song Y, Andreadis A, Fu Y, Brady ST, Binder LI. Pathogenic Forms of Tau Inhibit Kinesin-Dependent Axonal Transport through a Mechanism Involving Activation of Axonal Phosphotransferases. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2011;31(27):9858-68.