Regulation of Insulin Pathway Signaling in a Drosophila Model of ALS

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Amyotrophic Lateral Sclerosis is a fatal neurodegenerative disease. This disease involves the degeneration of upper and lower motor neurons and leads to loss of skeletal muscle function, eventually leading to death within a few years of diagnosis. In some patients (2-3%), mutations of TDP-43, an RNA binding protein, have been found. Notably, in a vast majority of all ALS cases, TDP-43 protein has been identified in proteinaceous aggregates within the cytoplasm of motor neurons. These findings implicate TDP-43 in the mechanisms underlying ALS. A Drosophila model was developed based on TDP-43 that demonstrates ALS pathophysiology including locomotor dysfunction, motor neuron degeneration, and decreased survival. This model was used previously in a drug screen to identify potential therapies and therapeutic targets. This screen identified thiazolidinediones and biguanides, two antidiabetic drugs known to affect insulin signaling, rescued lethality in the fly model. This indicates a relationship between TDP43 toxicity and the insulin signaling pathway. Here I investigate the possible involvement of TDP-43 in the phosphorylation of Akt and S6 Kinase, two key components of insulin signaling. To this end, I use western blots to investigate the effect of TDP-43 on phosphorylation of Akt and S6 Kinase. Results show that in the context of wild-type (TDP-wt) or mutant TDP-43 (i.e., TDP G298S9), Akt phosphorylation increased. Furthermore, S6 Kinase and 4-EBP phosphorylation are increased in TDP-wt genotype but not in G298S9 expressing motor neurons. Taken together, these results indicate that TDP-43 toxicity is involved in phosphorylation of Akt, 4-EBP, and S6 Kinase and they may be developed into a promising therapeutic target for ALS and related neurodegenerative diseases.