Drosophila p38 MAP kinase controls lifespan and locomotor coordination

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Determining how the genetic elements that contribute to neurodegenerative disease interact with environmental factors is imperative for our understanding of disease causality and progression. For instance, a key environmental factor that has been associated with Alzheimer's disease, Parkinson's disease, and ALS is oxidative stress, which is mediated by a variety of signaling pathways. One such genetically determined signaling pathway engaged by oxidative stress is the p38 MAP Kinase (p38K) cascade. However, mechanistic understanding of how p38K and oxidative stress contribute to neurodegenerative disease is sparse, due in part, to the complexity of the mammalian genome. Therefore, in my studies I have generated and utilized mutations in the two p38 kinase genes in the simpler genetic model system, *Drosophila*. My results show that lack of either p38Ka or p38Kb do not compromise viability, while complete loss of both is lethal. However, a strongly hypomorphic combination of p38Kb and p38Ka mutations results in decreased viability and a severely reduced lifespan. Interestingly, these defects can be rescued by ubiquitous or muscle specific expression of wild type p38Kb, or by the detoxifying enzyme SOD2. Furthermore, over expression of wild type p38Kb in muscles or neurons confers lifespan extension suggesting that p38K controls aging in flies, by regulating oxidative stress. Consistent with this, loss of p38K signaling results in age dependent locomotor behavior defects. Finally, I observe strong genetic interaction between p38K and *parkin* mutants. This, in addition to increased loss of dopaminergic neurons in p38K mutant brains, suggests a role for p38K signaling in PD, and supports the hypothesis that p38K signaling is a point of convergence for environmental stress and genetic factors that predispose towards neurodegeneration.