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Using *Drosophila* to define the role of glia in alpha-Synucleinopathies

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α-synucleinopathies are neurodegenerative diseases that are characterized pathologically by α- synuclein inclusions in neurons and glia. In spite of this, the role of glial α-synuclein and even glia more broadly in these diseases is not well understood. Glial α-synuclein may be of particular importance in multiple system atrophy (MSA), which is defined pathologically by glial cytoplasmic α-synuclein inclusions. We have previously described *Drosophila* models of neuronal α-synucleinopathy, which recapitulate key features of the human disorders. We have now expanded our model to express human α-synuclein in glia. We demonstrate that expression of α-synuclein in glia alone results in α-synuclein aggregation, death of dopaminergic neurons, impaired locomotor function, and autonomic dysfunction. Furthermore, co-expression of α- synuclein in both neurons and glia worsens these phenotypes as compared to expression of α- synuclein in neurons alone. We identify unique transcriptomic signatures induced by glial as opposed to neuronal α-synuclein. These results suggest that glial α-synuclein may contribute to the burden of pathology in the α-synucleinopathies through a cell type specific transcriptional program. This new *Drosophila* model system enables further mechanistic studies dissecting the contribution of glial and neuronal α-synuclein in vivo, potentially shedding light on mechanisms of disease that are especially relevant in MSA but also the α-synucleinopathies more broadly. Indeed, beyond glial α-synuclein, we identify additional novel glial modifiers of neuronal α- synuclein toxicity in the hopes of eventually turning these modifiers into glial-based therapeutics for Parkinson's disease

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