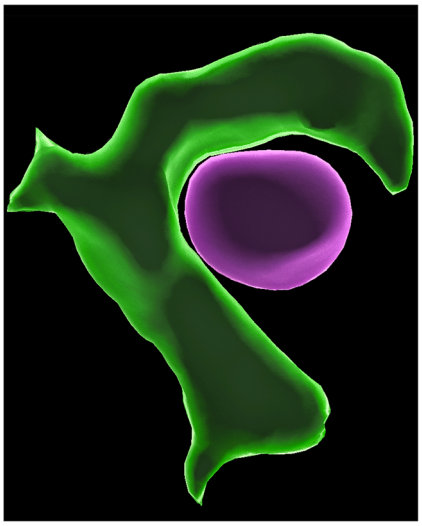
This Week in The Journal

Mechanistic Insight on Dysfunctional Glia in a Drosophila Model of Huntington's Disease

Graham H. Davis, Aprem Zaya, and Margaret M. Panning Pearce

(see article e1256232024)

Diseases characterized by neuron death, such as Huntington's disease (HD), are strongly associated with the buildup of misfolded proteins into amyloids. How amyloid aggregation leads to the loss of neurons remains unclear, but there is strong support for altered phagocytic glial cell activity promoting inflammation and the buildup and spread of amyloids. This has led to further investigation into how glial cells are altered in neurodegenerative disease states, with the end goal of understanding whether they can be targeted therapeutically to diminish aggregate spread. In this issue, Davis and colleagues used a *Drosophila* model of HD to investigate how HD pathophysiology impairs glial cell responsiveness. Glia in mutant huntingtin (mHTT)-containing *Drosophila* were not as responsive to injury and were less effective at degrading neuronal debris. Aggregation of mHTT in neurons upregulated innate immunity and phagocytic signaling pathways and caused accumulation of phagolysosomes in glia. A genetic screen revealed that the spread of mHTT aggregates from neurons to glia may be mediated by the GTPase Rab10. These findings provide important insight into mechanisms that contribute to dysregulated phagocytic glia activity in neurodegenerative states.



This image shows fluorescent protein-tagged Rab10 (green) expressed in glial cells partially surrounding an mCherry-tagged mHTT aggregate (magenta) that originated in an axon. Rab10 is a GTPase that associates with endosomes and phagosomes in cells. Image credit: G.H.D.

Integrating Modeling and Empirical Data to Understand FC-ERPs

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(see article e2016232024)

An effective way to understand the neural basis of behavior is by using data-driven computational modeling. Researchers typically use frontocentral event-related potentials (FC-ERPs) as correlates of cognition and motor control despite a generally poor understanding of these neural events. Herein, Diesburg and colleagues combined experimental data with simulations of neocortical cells and circuits to explore the underlying mechanisms of FC-ERPs with the end goal of enabling more accurate experimental interpretations. They measured human FC-ERPs with EEG after participants successfully or unsuccessfully stopped actions following stop-signals in the stop-signal behavioral task. They then used a neurophysiological model in the open-source Human Neocortical Neurosolver graphical user interface to match the outputs of simulated cell networks given external inputs onto cortical cells with FC-ERP waveforms from their empirical data. The authors discovered that it may be a specific sequence of inputs onto cortical cells that generate FC-ERPs during the stop-signal task. The model parameters that resulted from their experiments and analyses provide a basis for future work simulating mechanisms of FC-ERP in other behavioral contexts. This study also shows how the Human Neocortical Neurosolver can be used to better understand neural signatures underlying cognitive behaviors.

This Week in The Journal was written by Paige McKeon

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