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Palmitoylation-dependent control of neuronal ion channel clustering

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ALEX 100

Neuronal excitability predicts if a neuron fires an electrical impulse or not and precise control of neuronal excitability is essential for normal behaviour and cognition, while aberrant excitability is a hallmark of many neurological diseases. One key factor that controls the threshold of excitability is the clustering of voltage-gated ion channels at the Axon Initial Segment (AIS), the proximal part of the axon that regulates whether or not a neuron fires a nerve impulse to its neighbors. Modification with the lipid palmitate, through a process called palmitoylation, controls targeting of neurotransmitter receptors and associated 'scaffold' proteins to neuronal synapses and several palmitoyl acyltransferases (PATs) are implicated in this process. However, how palmitoylation controls targeting of proteins to the AIS in neurons is less well understood. I identified a PAT enzyme called ZDHHC14 as a direct interactor and regulator of scaffold proteins and potassium channels at the AIS. This is the first identification of a role for ZDHHC14 in neurons and the first description of palmitoylation-dependent control of AIS ion channel regulation. New data suggests other ion channels may also undergo similar palmitoylation-based regulation at the AIS and that alterations in neuronal activity drive rapid changes in palmitoylation of ion channels. These findings have broader implications for our understanding of physiological regulation of excitability and its dysfunction in conditions such as epilepsy.

Search Committee: Marc Coppolino, Chair; John Dawson; Steffen Graether; Ian Tetlow; Melissa Perreault; Morgan Stykel, Graduate Student; Todd Gillis, CBS Dean's Office