

Abstract Title: Neuronal Glycogen in Health and Disease: Lessons from Monogenic Disorders

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Abstract: Numerous studies on genetic disorders have led to the identification of novel cellular pathways and elucidating how abnormalities in these pathways result in the disease phenotype. Mitophagy (Parkinson's disease), protein aggregation and its transmission (Creutzfeldt-Jakob disease), post-transcriptional gene regulation, and the formation of stress granules (amyotrophic lateral sclerosis) are examples of such discoveries. Lafora disease, a fatal neurological disorder that affects adolescents and is caused by mutations in the genes coding for laforin protein phosphatase or malin E3 ubiquitin ligase, is another example in this growing list. In the past two decades, researchers have discovered a plethora of activities for these two proteins, as well as the mechanisms by which variations in these processes lead to neurodegeneration. The abnormal accumulation of glycogen in neurons and other tissues is a characteristic pathology of Lafora disease. These inclusions, known as Lafora bodies, are an abnormal, less branched, and water-insoluble form of glycogen. Studies have demonstrated that neurons possess the machinery necessary to synthesize glycogen despite the fact that they do not normally store a substantial amount of glycogen. Laforin and malin, two proteins deficient in Lafora disease, prevent glycogen accumulation in neurons. Therefore, neurodegeneration is caused by the functional loss of laforin or malin. In contrast, conditional deletion of glycogen synthase in neurons increases animal lifespan and improves neurological functions. In this talk, I will discuss the neuron-specific functions of glycogen and how the glycogen synthesis process can protect or kill neurons using observations from animal models of rare disorders.