Lafora disease ubiquitin ligase malin promotes proteasomal degradation of neuronatin and regulates glycogen synthesis.

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Abstract

Lafora disease (LD) is the inherited progressive myoclonus epilepsy caused by mutations in either EPM2A gene, encoding the protein phosphatase laforin or the NHLRC1 gene, encoding the ubiquitin ligase malin. Since malin is an ubiquitin ligase and its mutations cause LD, it is hypothesized that improper clearance of its substrates might lead to LD pathogenesis. Here, we demonstrate for the first time that neuronatin is a novel substrate of malin. Malin interacts with neuronatin and enhances its degradation through proteasome. Interestingly, neuronatin is an aggregate prone protein, forms aggresome upon inhibition of cellular proteasome function and malin recruited to those aggresomes. Neuronatin is found to stimulate the glycogen synthesis through the activation of glycogen synthase and malin prevents neuronatin-induced glycogen synthesis. Several LD-associated mutants of malin are ineffective in the degradation of neuronatin and suppression of neuronatin-induced glycogen synthesis. Finally, we demonstrate the increased levels of neuronatin in the skin biopsy sample of LD patients. Overall, our results indicate that malin negatively regulates neuronatin and its loss of function in LD results in increased accumulation of neuronatin, which might be implicated in the formation of Lafora body or other aspect of disease pathogenesis.