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Lysosomal dysfunction in neurodegeneration
The role of ATP13A2/PARK9

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Neuronal homeostasis and survival critically depend on an efficient autophagy-lysosomal degradation pathway, especially since neurons cannot reduce the concentration of misfolded proteins and damaged organelles by cell division. While increasing evidence implicates lysosomal dysfunction in the pathogenesis of neurodegenerative disorders, the molecular underpinnings of the role of lysosomes in neurodegeneration remain largely unknown. To this end, studies of neurodegenerative disorders caused by mutations in lysosomal proteins offer an opportunity to elucidate such mechanisms and potentially identify specific therapeutic targets. One of these disorders is Kufor-Rakeb syndrome, caused by mutations in the lysosomal protein ATP13A2/PARK9 and characterized by early-onset Parkinsonism, pyramidal degeneration and dementia. We found that loss of ATP13A2 function results in impaired lysosomal function and, consequently, accumulation of SNCA/α-synuclein and neurotoxicity. Our results suggest that targeting of ATP13A2 to lysosomes to enhance lysosomal function may result in neuroprotection in Kufor-Rakeb syndrome. From a broader perspective, these findings, together with other recent studies of lysosomal dysfunction in neurodegeneration, suggest that strategies to upregulate lysosomal function in neurons represent a promising therapeutic approach for neurodegenerative disorders.

Keywords: ATP13A2, lysosomal dysfunction, α-synuclein, Parkinsonism, neurodegeneration

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The autophagy-lysosomal pathway plays an important role in maintaining cellular homeostasis by degrading bulky cytoplasmic material including damaged organelles and misfolded and accumulated proteins. This degradation pathway appears crucial for clearance of aggregated proteins that represent a pathological hallmark of several neurodegenerative disorders, such as Parkinson, Huntington and Alzheimer diseases. In Parkinson disease (PD) and related synucleinopathies, accumulation of SNCA/α-synuclein plays a key role in disease pathogenesis. This is especially evident in some forms of familial PD, most notably in *SNCA* locus triplications and duplications where the expression levels of SNCA closely correlate with clinical phenotypes. In addition, lowering expression of SNCA in conditional mouse models leads to partial reversal of the observed pathological and behavioral phenotypes, further suggesting that efficient clearance of SNCA represents a key therapeutic target in synucleinopathies. While SNCA is degraded by both the ubiquitin-proteasome and autophagy-lysosomal system, it is the latter pathway that is important for clearance of aggregated SNCA. In order to study lysosomal function in synucleinopathies it is particularly informative to examine disorders that are caused by mutations in lysosomal proteins. To this end, identification of mutations in the lysosomal P5-type ATPase ATP13A2/PARK9 as the cause of Kufor-Rakeb syndrome (juvenile Parkinsonism, pyramidal degeneration, dementia) offered an opportunity to examine the molecular mechanisms of lysosomal function in this disorder. While the wild-type function of ATP13A2 remains largely unknown, recent studies showed that overexpression of ATP13A2 suppresses SNCA-mediated

toxicity in yeast and *C. elegans,* whereas ATP13A2 loss-of-function enhances SNCA misfolding in body wall muscle cells in a *C. elegans* model of PD. These data implicate ATP13A2 in SNCA misfolding and toxicity, but the underlying mechanism has not been established. Mutations in ATP13A2 result in misfolding and destabilization of the protein in the endoplasmic reticulum that presumably results in deficiency of ATP13A2 in lysosomes. To model ATP13A2 loss of function, we used RNAi to silence the protein in mouse primary neurons and examined lysosomal function. These experiments revealed accumulation of enlarged lysosomes, impaired lysosomal turnover of autophagic vesicles and impaired lysosomal degradation capacity upon silencing of *ATP13A2*. Similar results were obtained in fibroblasts from patients with Kufor-Rakeb disease, suggesting that loss of ATP13A2 function accurately models disease pathogenesis. Importantly, restoration of ATP13A2 partially reverses these lysosomal alterations, further suggesting the importance of ATP13A2 function for lysosomal function.

Since previous studies suggested that ATP13A2 plays a role in SNCA misfolding and toxicity in *C. elegans* and yeast, we examined a possible mechanistic link in neurons. To this end, we demonstrated that diminished lysosomal degradation in ATP13A2-depleted neurons results in preferential accumulation of endogenous SNCA, highlighting the importance of proper lysosomal function for the turnover of SNCA. Furthermore, we found that depletion of endogenous SNCA diminishes the toxicity in ATP13A2-deficient neurons, suggesting that neurotoxicity due to loss of ATP13A2 function is at least partially mediated by lysosomal dysfunction and consequent accumulation of SNCA.

We have previously shown that mutations in the lysosomal enzyme glucocerebrosidase (GC) that cause Gaucher disease also result in decreased lysosomal degradation capacity and accumulation of SNCA. A decrease in GC lysosomal activity leads to accumulation of its lipid substrates that interact with SNCA and enhance its aggregation. While it is not known if similar lipids accumulate in ATP13A2-deficient neurons, this possibility is unlikely since ATP13A2 presumably functions as an ion pump that regulates cation homeostasis. However, both ATP13A2 and GC loss-of-function mutations result in lysosomal dysfunction and accumulation of SNCA. We hypothesize that high concentrations of SNCA in neurons and its propensity for aggregation make it a preferential substrate for accumulation in neurons that exhibit lysosomal dysfunction. This process is likely accelerated in the presence of accumulated lipids that directly interact with SNCA and enhance its aggregation. While the precise mechanism of neurodegeneration in Kufor-Rakeb syndrome remains unknown, our data suggest that ATP13A2 mediates neurotoxicity at least partially via lysosomal dysfunction and accumulation of SNCA. This view is supported by our observation that ATP13A2-deficient neurons require the presence of endogenous SNCA to exhibit maximal toxicity. Since lysosomes also play a key role in degradation of dysfunctional organelles, it will be of interest to examine whether GC- or ATP13A2-mediated lysosomal dysfunction results in accumulation and dysfunction of cellular organelles. To this end, the Klein laboratory recently demonstrated that loss-of-function mutations in ATP13A2 cause accumulation of fragmented mitochondria, suggesting disrupted mitochondrial clearance via lysosomes. Similarly, the Chu group proposed that decreased autophagy associated with ATP13A2 deficiency affects mitochondrial quality control, resulting in increased ROS production. These data implicate loss of ATP13A2 function in mitochondrial maintenance and oxidative stress, lending further support to converging lysosomal and mitochondrial pathways in PD pathogenesis. Interestingly, the group of Guerreiro identified *ATP13A2* homozygous mutation in a family with pathology typical for neuronal ceroid lipofuscinoses (NCLs), a heterogeneous group of lysosomal storage diseases that present with the accumulation of lipopigments, and neurodegeneration. These data suggest that NCLs and Kufor-Rakeb syndrome share etiological features and further implicate the lysosomal pathway in Parkinson disease.

In summary, our recent study suggests that lysosomal dysfunction and accumulation of SNCA plays an important role in the pathogenesis of Kufor-Rakeb syndrome and highlights the upregulation of lysosomal degradation capacity as a novel therapeutic strategy in PD and other neurodegenerative disorders.