Mannose 6-Phosphate Receptor Is Reduced in α-Synuclein Overexpressing Models of Parkinson's Disease

Increasing evidence points to defects in autophagy as a common denominator in most neurodegenerative conditions. Progressive functional decline in the autophagy-lysosomal pathway (ALP) occurs with age, and the consequent impairment in protein processing capacity has been associated with a higher risk of neurodegeneration. Defects in cathepsin D (CD) processing and α-synuclein degradation causing its accumulation in lysosomes are particularly relevant for the development of Parkinson's disease (PD). However, the mechanism by which alterations in CD maturation and α-synuclein degradation leads to autophagy defects in PD neurons is still uncertain. Here we demonstrate that MPR300 shuttling between endosomes and the trans Golgi network is altered in α-synuclein overexpressing neurons.

Consequently, CD is not correctly trafficked to lysosomes and cannot be processed to generate its mature active form, leading to a reduced CD-mediated α-synuclein degradation and α-synuclein accumulation in neurons. MPR300 is downregulated in brain from α-synuclein overexpressing animal models and in PD patients with early diagnosis. These data indicate MPR300 as crucial player in the autophagy-lysosomal dysfunctions reported in PD and pinpoint MRP300 as a potential biomarker for PD.

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