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Abstract Book

The nucleotide exchange factor BAG1 prevents neurotoxic misfolded proteins accumulation via proteasome and chaperone mediated autophagy.

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Muscle and motor neuron disorders

Protein quality control system maintains protein homeostasis in humans preventing protein aggregation and toxicity by enhancing their degradation via proteasome and/or autophagy.

Different disease associated proteins, such as SOD1 and TDP-43 in familial and sporadic amyotrophic lateral sclerosis and frontotemporal dementia, or androgen receptor (AR) in spinal and bulbar muscular atrophy, tend to misfold and accumulate into aggregates in neurons. An efficient dynein mediated transport of misfolded proteins to the site of degradation is required as key point to control their aggregation and degradation. In fact, when we blocked the dynein retrograde transport, we found an alteration of SQSTM1/p62 and LC3 expression and localization and a reduction of autophagosome number per cell. Despite this, blockage of dynein function reduced the PBS insoluble fraction of mutated misfolded proteins. Dynein inhibition selectively increased the mRNA level of the nucleotide exchange factor BAG1 both in NSC34 and in motoneuron derived from iPS cells. Notably, exogenous BAG1 overexpressionreduced misfolded species aggregation in a UPS dependent manner.

Moreover, dynein inhibition increased mRNA and protein levels of the chaperone mediated autophagy (CMA) receptor Lamp2A, suggesting that CMA can restore misfolded proteins degradation via their KFERQ-like motif and are internalized into lysosome by Lamp2A. Indeed dynein inhibition, BAG1 mRNA is increased also in Lamp2A depleted cells. To study CMA, we measured synuclein protein as CMA substrate. We found that BAG1 overexpression reduced synuclein level, while BAG1 depletion has an opposite effect. In parallel Lamp2A depleted cells presented a very efficient proteasome system that rapidly efficiently cleared soluble synuclein, even if we observed a synuclein insoluble accumulation in filter retardation assay.

Collectively, these data suggest that BAG1 is an important player to assist misfolded protein degradation via proteasome or CMA.

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