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YMS02 Young Members' Symposia 2

YMS02-01

BAG1 prevents misfolded proteins accumulation when autophagy flux is blocked in neurodegenerative disorders

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Different disease associated proteins, 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. Protein quality control system prevents their aggregation and toxicity by enhancing their degradation via proteasome and/or autophagy. An efficient dynein mediated transport of misfolded proteins to the site of degradation is required as key point to control their aggregation and degradation. HSPB8 is a protective protein that reduces disease associated proteins aggregation by autophagy facilitation. Here we evaluated the HSPB8 effects on the recently discovered RAN translated poly-di-peptides (DPRs) from C9ORF72 gene. Using filter trap and western blot we observed that HSPB8 over-expression facilitates DPRs clearance even when proteasome is blocked. when we blocked the dynein retrograde transport by EHNA we found an alteration of SQSTM1/p62 and LC3 expression and localization. However, dynein inhibition reduced SQSTM1/p62 and LC3 levels induced by trehalose and drastically reduced the number of autophagosome per cell. Moreover, EHNA reduced the PBS insoluble fraction of mutated misfolded proteins and DPRs also when autophagy is blocked. This effect was counteracted by proteasome inhibition. Notably, EHNA selectively increased BAG1 mRNA (responsible for misfolded protein degradation via proteasome) in NSC34 and motoneuron derived from iPS cells, while exogenous BAG1 overexpression reduced misfolded species aggregation and BAG1 down-regulation blocked the EHNA effect. Moreover, EHNA increased mRNA and protein levels of chaperone mediated autophagy receptor Lamp2A, suggesting that CMA can restore the degradation of misfolded proteins with KFERQ-like motif that are internalized into lysosome by Lamp2A. Collectively, these data suggest that when autophagy flux is blocked, misfolded proteins can be re-routed by BAG1 to alternative degradative pathways.

YMS02-02

A novel avenue for protection against tauopathy: ADNP/NAP dramatically increase microtubule end-binding protein-tau interaction

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Background: Activity-dependent neuroprotective protein (ADNP), vital for brain formation and cognitive function, is mutated in autism and linked to neurodegenerative/psychiatric diseases. An eight-amino-acid peptide snippet of ADNP, NAP (NAPVSIPQ), identified as a smallest active fragment, includes the SxIP microtubule (MT) end-binding protein (EB) association motif, and enhances ADNP-EB3 interaction. Depletion of EB1 or EB3 abolishes NAP protection against zinc intoxication. Furthermore, NAP enhances Tau-MT interaction, and Tau regulates the localization and function of EB1 and EB3 in developing neuronal cells.
Aims: To reveal how NAP (ADNP) enhances Tau-MT interactions and whether this is mediated by EBs.
Methods: NAP impact on the EB's morphology and dynamics was estimated by immunofluorescence and time-lapse imaging, EB-Tau and EB/Tau-MT interactions - by Co-Immunoprecipitation and Polimeryzed vs. Solible tubulin assay in the differentiated N1E-115 cells.
Results: We showed, for we believe the first time, that NAP augmented endogenous EB1 comet density in the N1E-115 neuroblastoma neuronal model. This finding was substantiated by cell transfection with fluorescent EB1 and live cell imaging. NAP increased comet amounts, length and speed. At the molecular level, NAP enhanced EB3 homodimer formation, while decreasing EB1-EB3 heterodimer content and driving EB1- and EB3-Tau interactions (dramatic 20-fold increases), leading to recruitment of EB1/EB3 and Tau to MTs under zinc intoxication. NAP did not protect NIH3T3 cells against zinc intoxication, unless these cells were transfected with Tau.
Conclusions: EB-Tau interaction is identified as a novel target for endogenous ADNP neuroprotection, and a future target for drug development, with NAP as a prototype. (Molecular Psychiatry, 2017; https://doi.org/10.1038/mp.2016.255).