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A ROLE FOR SMALL UBIQUITIN-LIKE MODIFIER (SUMO-1) IN THE AUTOPHAGIC RESPONSE TO PROTEIN AGGREGATES IN NEURODEGENERATION

Pountney D.L.
Griffith Health Institute and School of Medical Science, Griffith University, Gold Coast, Australia.

Many neurodegenerative diseases are characterised by microscopically-visible protein aggregates, or inclusion bodies, within neural cells. Initially found in intranuclear inclusions in hereditary ataxias and Huntington's disease, the ubiquitin homologue, SUMO-1, has now been shown in a range of neurodegenerative diseases in both nuclear and cytoplasmic inclusions, and marks sub-domains in Lewy bodies and in glial cytoplasmic α-synuclein inclusions. Proteomic analysis of intranuclear inclusion bodies revealed that SUMO-1 was associated with proteins of the endomembrane system. In recent studies, we have found that SUMO-1 is associated with lysosomes both in neurodegenerative diseases and in rodent and cellular disease models. We examined brain tissue from cases of progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and normal controls and identified co-localisation of the lysosomal marker, cathepsin D, and SUMO-1 associated with both the tau-positive PSP inclusions and the α-synuclein-positive MSA inclusions. Rat and mouse models of Parkinson's disease were investigated that employ unilateral injection of the mitochondrial complex 1 inhibitor, rotenone and revealed the association of SUMO-1 with lysosomes and α-synuclein intracellular inclusion bodies in the lesioned brain tissue. The OLN oligodendrocyte cell model recapitulates PSP-like tau inclusions and showed associated SUMO-1-positive lysosomes. SUMO-1-positive lysosomes were also associated both with polyglutamine aggregates in Httexon1-Q74-eGFP transfected cells and with α-synuclein aggregates in α-synuclein over-expressing cells. Western analysis of purified lysosomes revealed an increase of SUMO-1 in the lysosomal fraction. These findings suggest a role for SUMO-1 in the autophagy pathway in neurodegeneration.