Abstract: The Effect Of Mahogunin On Lysosomal Pathways In Prion Mediated Spongiform Neurodegeneration

Lysosome is the terminal degradative organelle of the cells. Autophagy and endocytosis are considered to be two important arms of lysosomal degradative pathway. Defects in both or either of these pathways are common in different neurodegenerative diseases. Prion diseases are characterized by spongiform neurodegeneration. Prion protein is a cell surface glycoprotein, aberrant metabolism of which leads to either transmissible (acquired via a misfolded isoform of the PrP termed PrPSc), or familial (inherited through PrP mutations that may increase generation of a minor PrP isoform, CmpPrP) Prion diseases. Cytosolic E3 ligase, Mahogunin Ring Finger-I (MGRN1) has been reported to interact with CmpPrP, resulting in dysfunctional lysosomes.

The present study reports that depletion of MGRN1 leads to blocked fusion of lysosomes with amphisomes and multivesicular bodies and thereby affecting both autophagic and endocytic pathway.

Depletion of MGRN1 leads to an enlargement in the size of late-endosomes and lysosomes along with increase in the levels of autophagy markers, detected in cell lines and brain lysates from transgenic mice (with abundance of CmpPrP). Both autophagic flux and degradation competence are affected. The impaired fusion between autophagosomes (via amphisomes) with lysosomes leads to accumulation of amphisomes. Simultaneously, while formation of multivesicular bodies is unaffected, their fusion with lysosomes is perturbed. Interestingly, all these phenotypes could be rescued by over-expression of ESCRT-I protein TSG101 and its monoubiquitination. Therefore ESCRT-I protein, TSG101, plays an important role in the regulation of late fusion events of the lysosomal degradative pathway. TSG101 is primarily shown to be involved in the formation of endosomes. This study for the first time shows participation of TSG101 in generation of amphisome-lysosome and MVB-lysosome hybrid organelles. MGRN1 in turn regulates TSG101 through its monoubiquitination. This posttranslational modification affects vesicular fusion events and clearance of cargo brought in by the two arms of lysosomal degradation (autophagy and endocytosis).

Thus my study for the first time shows that by regulating both the autophagosomal and endo-lysosomal degradation pathways, MGRN1 could govern spongiform neurodegeneration in some types of prion disease.

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