Targeting autophagy in ALS: A complex mission

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Several neurodegenerative diseases share a common neuropathology, primarily featuring the presence of abnormal protein inclusions in the brain containing specific misfolded proteins. Strategies to decrease the load of protein aggregates and oligomers are considered relevant targets for therapeutic intervention. Many studies indicate that macroautophagy is a selective and efficient mechanism for the degradation of misfolded mutant proteins related to neurodegeneration, without affecting the levels of the corresponding wild-type form. In fact, activation of autophagy by rapamycin treatment decreases the accumulation of protein aggregates and alleviates disease features in animal models of Huntington disease and other disorders affecting the nervous system. Recent evidence, however, indicates that the expression of several disease-related genes may actually impair autophagy activity at different levels, including omegasome formation, substrate recognition, lysosomal acidity and autophagos