THE ROLE OF ALZHEIMER’S DISEASE-ASSOCIATED UBIQUITIN-1 TRANSCRIPT VARIANTS IN PRESENILIN-1 ACCUMULATION AND AGGRESOME FORMATION


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Introduction: Alzheimer’s disease (AD)-associated ubiquitin-1 regulates the levels and proteasomal degradation of several neurodegenerative disease-associated proteins, including presenilin-1 (PS1).

Aims: We characterized here the effects of ubiquitin-1 transcript variants (TV), the full-length TV1 and TV3 lacking the proteasome-interaction domain, on the levels and subcellular localization of PS1.

Methods: PS1 and TV1 or TV3 cDNAs were transfected to human embryonic kidney HEK293, neuronal SH-SY5Y, or mouse primary cortical cells. Western blotting, fluorescence, electron (EM) or fluorescence lifetime microscopy, γ-secretase activity measurement, and Aβ enzyme-linked immunosorbent assay were employed in the analyses. HEK293T-UbG76V-yellow fluorescent protein reporter cells were used to study ubiquitin/proteasome system (UPS) function.

Results: Co-expression of TV3 with PS1 prominently induced high-molecular-weight PS1 accumulation, stabilization of full-length PS1 levels, and PS1 and TV3 co-localization in aggresomes. Also PS1 and TV1 co-localized in aggresomes in TV1-overexpressing cells. Quantification demonstrated that the formation of PS1-positive aggresomes was significantly increased in cells co-expressing PS1 with TV1 or TV3 compared to cells overexpressing PS1 alone. EM confirmed the presence of TV1 and TV3 in aggresomes and autophagosomes. These effects were not caused by a general UPS impairment in TV1- or TV3-overexpressing cells. Moreover, PS1 accumulation and aggresome formation coincided with altered Aβ levels particularly in TV3-overexpressing cells, but this was not due to changed γ-secretase activity or PS1 binding to TV3.

Conclusions: Our results suggest that specific ubiquitin-1 TVs regulate PS1 accumulation and targeting into aggresomes and autophagosomes. Thus, alternative splicing may be an important regulator of ubiquitin-1 function also in AD pathogenesis.