

P066 The novel Alzheimer's disease-associated protein ubiquilin-1 regulates presenilin-1 aggregation and formation of aggresomes.

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The ubiquitin-like protein ubiquilin-1 is genetically and functionally associated to Alzheimer's disease (AD) and it regulates proteasomal degradation of proteins including AD-associated presenilin-1 (PS1). Ubiquilin-1 may also play a role in other neurodegenerative diseases involving abnormal protein aggregation. Here we characterized the role of ubiquilin-1 transcript variants (TV) in protein aggregation and ubiquitin-proteasome system (UPS) in HEK293 cells. We found that full-length ubiquilin-1 TV1 and TV3, which lacks the proteasome interaction domain, induced accumulation and aggregation of high-molecular-weight PS1 fragments. Additionally, formation of aggresome-like structures significantly increased in cells overexpressing PS1 and TV1 or TV3 as compared to control cells. These effects were most prominent in TV3-expressing cells. Both the proteins co-localized in the aggresomes. Moreover, characteristic of aggresomes, the intermediate filament protein vimentin redistributed to the aggresomal structures. Overexpression of TV1 or TV3 did not cause a general impairment of the UPS. Collectively, our results suggest that ubiquilin-1 regulates PS1 aggregation and aggresome formation, which may partially contribute to AD pathogenesis.