ESCRT-III dysfunction causes autophagosome accumulation and neurodegeneration.

Journal: Curr Biol
Publication Year: 2007
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PubMed link: 17683935
Funding Grants: Gladstone CIRM Scholar Program

Public Summary:
Defects in the endosomal-lysosomal pathway have been implicated in a number of neurodegenerative disorders. A key step in the endocytic regulation of transmembrane proteins occurs in a subset of late-endosomal compartments known as multivesicular bodies (MVBs), whose formation is controlled by endosomal sorting complex required for transport (ESCRT). The roles of ESCRT in dendritic maintenance and neurodegeneration remain unknown. Here, we show that mSnf7-2, a key component of ESCRT-III, is highly expressed in most mammalian neurons. Loss of mSnf7-2 in mature cortical neurons caused retraction of dendrites and neuronal cell loss. mSnf7-2 binds to CHMP2B, another ESCRT-III subunit, in which a rare dominant mutation is associated with frontotemporal dementia linked to chromosome 3 (FTD3). Ectopic expression of the mutant protein CHMP2B(Intron5) also caused dendritic retraction prior to neurodegeneration. CHMP2B(Intron5) was associated more avidly than CHMP2B(WT) with mSnf7-2, resulting in sequestration of mSnf7-2 in ubiquitin-positive late-endosomal vesicles in cortical neurons. Moreover, loss of mSnf7-2 or CHMP2B(Intron5) expression caused the accumulation of autophagosomes in cortical neurons and flies. These findings indicate that ESCRT-III dysfunction is associated with the autophagy pathway, suggesting a novel neurodegeneration mechanism that may have important implications for understanding FTD and other age-dependent neurodegenerative diseases.

Scientific Abstract:
Defects in the endosomal-lysosomal pathway have been implicated in a number of neurodegenerative disorders. A key step in the endocytic regulation of transmembrane proteins occurs in a subset of late-endosomal compartments known as multivesicular bodies (MVBs), whose formation is controlled by endosomal sorting complex required for transport (ESCRT). The roles of ESCRT in dendritic maintenance and neurodegeneration remain unknown. Here, we show that mSnf7-2, a key component of ESCRT-III, is highly expressed in most mammalian neurons. Loss of mSnf7-2 in mature cortical neurons caused retraction of dendrites and neuronal cell loss. mSnf7-2 binds to CHMP2B, another ESCRT-III subunit, in which a rare dominant mutation is associated with frontotemporal dementia linked to chromosome 3 (FTD3). Ectopic expression of the mutant protein CHMP2B(Intron5) also caused dendritic retraction prior to neurodegeneration. CHMP2B(Intron5) was associated more avidly than CHMP2B(WT) with mSnf7-2, resulting in sequestration of mSnf7-2 in ubiquitin-positive late-endosomal vesicles in cortical neurons. Moreover, loss of mSnf7-2 or CHMP2B(Intron5) expression caused the accumulation of autophagosomes in cortical neurons and flies. These findings indicate that ESCRT-III dysfunction is associated with the autophagy pathway, suggesting a novel neurodegeneration mechanism that may have important implications for understanding FTD and other age-dependent neurodegenerative diseases.

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