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TorsinA protein degradation and autophagy in DYT1 dystonia

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Abstract

Early-onset generalized dystonia (DYT1) is a debilitating neurological disorder characterized by involuntary movements and sustained muscle spasms. DYT1 dystonia has been associated with two mutations in torsinA that result in the deletion of a single glutamate residue (torsinA ΔE) and six amino-acid residues (torsinA Δ323-8). We recently revealed that torsinA, a peripheral membrane protein, which resides predominantly in the lumen of the endoplasmic reticulum (ER) and nuclear envelope (NE), is a long-lived protein whose turnover is mediated by basal autophagy. Dystonia-associated torsinA ΔE and torsinA Δ323-8 mutant proteins show enhanced retention in the NE and accelerated degradation by both the proteasome and autophagy. Our results raise the possibility that the monomeric form of torsinA mutant proteins is cleared by proteasome-mediated ER-associated degradation (ERAD), whereas the oligomeric and aggregated forms of torsinA mutant proteins are cleared by ER stress-induced autophagy. Our findings provide new insights into the pathogenic mechanism of torsinA ΔE and torsinA Δ323-8 mutations in dystonia and emphasize the need for a mechanistic understanding of the role of autophagy in protein quality control in the ER and NE compartments.

Keywords

Dystonia; autophagy; torsinA; endoplasmic reticulum-associated degradation; endoplasmic reticulum; nuclear envelope; protein misfolding; protein quality control

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torsinA ΔE and torsinA Δ323-8 mutations in a neuronal cell-type-specific manner. These data suggest that, in addition to functioning in the ER of both neuronal and non-neuronal cells, torsinA has a neuron-specific role in the NE, which is consistent with the neuronal NE phenotype of torsinA knockout and torsinA ΔE knock-in mice. The precise function of torsinA in the ER and NE remains unknown, although torsinA has been proposed to act as a molecular chaperone for regulating the organization of the ER and NE compartments or protein trafficking through the ER.

Our study revealed that torsinA WT is a very stable protein with a half-life of ~3.5 days. Previous studies have shown that most ER resident proteins have a long half-life, in the order of 2 to 6 days, although a small number of ER resident proteins have a much shorter half-life. The mechanism governing the normal turnover of ER resident proteins remains unclear. We found that torsinA WT is degraded by autophagy but not the proteasome. Our data raises the possibility that torsinA WT and other long-lived ER resident proteins may segregate in a subdomain of the ER which is targeted for degradation by basal autophagy (Fig. 1B).

Our study indicated that torsinA ΔE and torsinA Δ323-8 mutations destabilize torsinA considerably, reducing the half-life to ~18 h. These findings suggest that dystonia-associated mutations induce misfolding of torsinA into non-native conformations that can be recognized and selected by the cellular protein quality-control machinery for destruction. We found that, unlike torsinA WT, both torsinA ΔE and torsinA Δ323-8 mutants are degraded by the proteasome. It is unclear how torsinA mutants are specifically recognized and transported to the proteasome for degradation. One possibility is that dystonia mutation-induced torsinA folding defects are selectively recognized by an ER chaperone or E3 ubiquitin-protein ligase, which cooperates with other components of the ER-associated degradation (ERAD) system to facilitate retrotranslocation of torsinA mutants from the ER lumen to the cytosol for degradation by the cytosolic proteasome (Fig. 1B). The NE-localized torsinA mutant proteins might be retrotranslocated from the NE lumen to the nucleus by the inner nuclear membrane-associated ERAD for degradation by the nuclear proteasome (Fig. 1B), as shown for some mutant NE proteins in yeast. Alternatively, the NE-localized torsinA mutants might be retrotranslocated to the cytosol by the outer nuclear membrane-associated ERAD or they might have to migrate to the ER prior to ERAD-mediated retrotranslocation for degradation by the cytosolic proteasome (Fig. 1B).

Although the proteasome plays an important role in the clearance of torsinA mutants, proteasome activity does not fully account for their disposal. We found that the degradation of both torsinA ΔE and torsinA Δ323-8 mutants is also mediated by autophagy. Our data support the emerging view that autophagy provides an alternative ER quality control system for disposal of misfolded proteins. It has become clear that oligomeric and aggregated proteins are resistant to proteasomal degradation and can actually impair the proteasome function. Our finding that torsinA mutants are degraded by both the proteasome and autophagy raises the possibility that the monomeric form of torsinA mutants are cleared by proteasome-mediated ERAD, whereas the oligomeric and aggregated forms of torsinA mutants are cleared by autophagy.

Recent evidence suggests that ER stress resulting from accumulation of misfolded proteins can induce a specific type of autophagy, termed reticulophagy or ER-phagy, which selectively sequesters portions of the ER for lysosomal degradation.
autophagosome membrane for sequestering ER fragments remains unclear, but the ER has been proposed to be a membrane source for autophagosome formation.26, 27 It is possible that the oligomeric and aggregated forms of torsinA mutants may segregate in a specialized area of the ER which is engulfed and cleared by ER stress-induced reticulophagy (Fig. 1B). The role of autophagy in the quality control of the NE compartment remains unknown. In yeast, a process known as piece-meal microautophagy of the nucleus (PMN) is used to target portions of the NE for degradation by the vacuole, the yeast equivalent of the mammalian lysosome.28, 29 It is tempting to speculate that the NE-localized torsinA mutant proteins might be cleared by an autophagy process that is analogous to PMN or reticulophagy (Fig. 1B). Further investigation of the molecular pathways controlling the degradation of dystonia-associated torsinA mutants should advance our knowledge of the protein quality control mechanisms in the ER and NE, and facilitate the development of new therapeutic strategies for treating dystonia.

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References


**ABBREVIATIONS**

**DYT1**
- Early onset generalized dystonia

**WT**
- Wild-type

**ER**
- Endoplasmic reticulum

**NE**
- Nuclear envelope

**ERAD**
- Endoplasmic reticulum-associated degradation

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Figure 1.
Degradation of torsinA wild-type (WT) and mutant proteins by autophagy. (A) Domain structure of TorsinA. $S$, ER signal sequence; $H$, hydrophobic domain; $AAA^+$, ATPases associated with a variety of cellular activities. The locations of dystonia-associated torsinA mutations are indicated on the domain structure. (B) Potential mechanisms for clearance of torsinA WT and mutant proteins. TorsinA WT is recruited to a subdomain of the ER that is sequestered into an autophagosome for lysosomal degradation by basal autophagy. The ER-localized, monomeric form of torsinA mutant proteins are retrotranslocated to the cytosol by ERAD for degradation by the cytosolic proteasome, whereas the nuclear envelope (NE)-localized, monomeric form of torsinA mutant proteins may be retrotranslocated to the nucleus by the inner nuclear membrane-associated ERAD for degradation by the nuclear proteasome. It is also possible that the NE-localized torsinA mutant monomers are retrotranslocated to the cytosol by the outer nuclear membrane-associated ERAD or the mutants may have to migrate to the ER for ERAD-mediated degradation by the cytosolic proteasome. The ER-localized, oligomeric and aggregated forms of torsinA mutant proteins may segregate in a specialized

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area of the ER for clearance by ER stress-induced autophagy, whereas the NE-localized, oligomeric and aggregated forms of torsinA mutant proteins may be cleared by autophagy via an unknown mechanism.