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Review

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The role of the tubular endoplasmic reticulum in the axonal degeneration associated with neurodegenerative disorders

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Abstract

Neurodegenerative disorders represent a group of aging-related diseases affecting the different parts of the central nervous system. Axonal degeneration is among the leading causes of morbidity and disease progression in Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and other neurogenerative disorders. The unique structures of axons may make them particularly vulnerable to internal homeostasis. The axonal endoplasmic reticulum (ER) has emerged as one of the most important hallmarks in those neurodegenerative disorders associated with dysfunction of axonal transport, lipid synthesis, calcium dynamics, and interactions with other organelles. In this review, we summarize the role of tubular ER and its resident proteins in axonal degeneration, which emerges as an early pathological event in the axonal degeneration process. We also discuss the potential relationship between autophagy and tubular ER. With this review, we can consolidate the recent research advances in the role of tubular ER in axonal degeneration associated with several major neurodegenerative disorders and improve our understanding of axon pathophysiology and potential target therapies.

Keywords: Tubular endoplasmic reticulum, axonal degeneration, neurodegenerative disorders

INTRODUCTION

The morpho-functional organization of matured neurons is divided into the soma, dendrites, and axons. Dendrites are branched extensions that extend radially from the soma and receive synaptic inputs, whereas axons are longer and thinner projections that create action potentials and send them to the presynaptic terminal for neurotransmitter release. Axonal degeneration, featured by axonal swellings and axonal fragments, is a pathological hallmark of many neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic lateral sclerosis (ALS)[1-3]. Axons disintegrate in various ways, depending on the biological context. Local axonal degeneration is characterized by axon disintegration into separated axonal fragments. Injured axons may degenerate retrogradely (distal to proximal direction), anterogradely (proximal to distal direction), or in a Wallerian degeneration pattern (the distal part of the axon from the injury site), resulting in axonal fragments. Axonal swellings (axonal beadings, bubblings, or spheroids) are hallmarks of degenerating axons, which contain a disorganized cytoskeleton and organelles resulting from an interruption of axonal transport[4]. Axonal swellings usually precede axon fragmentation[5], and they are considered an early pathological event in AD[6], PD[7], and ALS[8].

The contents of swollen axons vary depending on the specific neurodegenerative disorder. In a mouse model of PD, small axonal swellings called globules have been observed, which contain autophagosome-like membranes[7]. In PD and Lewy body dementia, the presynaptic axon terminal in the dentate hippocampus has been found to contain α-, β-, and γ-synuclein[9]. In AD, axonal dystrophy can lead to swellings in both dendrites and axons, and the β-site APP-cleaving enzyme 1 (BACE1) has been observed to accumulate in axonal swellings when axonal trafficking is disrupted[6]. Galectin-1, a member of the β-galactoside-binding lectin family, accumulates in motor axonal spheroids and colocalizes with aggregated neurofilaments before developing ALS-like symptoms and is associated with early processes of axonal degeneration in $SOD1^{G93A}$ mice[8].

Although neurodegenerative disorders involve a wide range of axonal degenerative characteristics, they may share a common pathogenetic pathway. In particular, intracellular organelles play a critical role in maintaining axonal and microdomain functions. Evidence from eukaryotic cell studies suggests that ER regulates many intracellular biological activities. However, the importance and significance of ER in axons are only now recognized. Recently, tubular ER has attracted attention for its biological distribution and role in axonal homeostasis[10-12]. Axonal ER comprises tubular ER and forms a network of interconnected tubular structures, participating in axonal morphology, transport, and material metabolism, suggesting its potential role in neurodegeneration. Axonal degeneration may originate from the dysfunction of axonal ER in neurodegenerative disorders, and tubular ER proteins and dysfunctional tubular ER accumulate in axonal swellings[10-12]. Mutations in ER-shaping proteins cause neurodegenerative diseases such as hereditary spastic paraplegias (HSPs). Hereby we will discuss the biological function of tubular ER and its role in axonal degeneration in neurodegenerative disorders, including AD, ALS, PD, HSPs, and Huntington's disease (HD).

AXONAL TUBULAR ER STRUCTURAL CHARACTERISTICS AND BIOLOGICAL REGULATORY FUNCTIONS

Intracellular organelles maintain the functions of axons and microdomains. Evidence suggests that the ER regulates intracellular calcium levels, lipid synthesis, protein translation, quality control, and trafficking and

interacts with other membrane-bound organelles such as mitochondria, vesicles, and endosomes[13]. The axonal tubular ER is a specialized structure found in the neuronal axons. It is characterized by its long, narrow, and highly interconnected tubular structure, which extends throughout the entire length of axons[14]. This unique structure allows the axonal tubular ER to regulate several biological processes critical for axonal function and neuronal communication. The axonal tubular ER network is considered to be part of the ER throughout the neuron. Understanding the axonal network and the biological function may contribute to uncovering the pathogenesis of a variety of neurodegenerative disorders. However, scientists have only recently begun to comprehend the relevance of the structural properties of axonal tubular ER, its biological function, and axonal tubular ER regulation.

The structural characteristics of axonal tubular ER

The ER structure is highly conserved in eukaryotes, including neurons. The ER has the most surface area of any organelle found in eukaryotic cells. In light of the fact that the surface area of neurons is, on average, four orders of magnitude larger than that of other tiny and less polarized cells, the expansion of the neuronal ER represents a remarkable evolutionary accomplishment[14]. ER is a pervasive and continuous membrane-bound system throughout the cytoplasm of all eukaryotic cells[15,16]. The neuronal ER consists of three components: nuclear envelope, the ribosome-rich rough ER, and the ribosome-devoid smooth ER[17,18]. Neuronal ER forms a continuous network of tubules and cisternae that extends throughout all cell compartments, including neuronal dendrites and axons. This network is capable of communicating with the majority of the cell's other organelles through the use of vesicular transport as well as through contacts that do not result in fusion but facilitate cross-talk across adjacent bilayers[19].

The axonal ER exhibits a significantly high surface-to-volume ratio among cellular compartments. However, it is unclear how this massive amount of ER membrane is arranged in axons to maintain function[20]. The tubular ER, which primarily resides in the peripheral region of cell, is a complex network of smooth ER that consists of interconnected tubules, typically 50 nm in diameter in mammals, interspersed with occasional and irregularly spaced sheets or cisternae characterized by larger and less regular lumens[21]. In neurons, the axonal ER comprises a tubular ER, forming a network of interconnected structures[11]. The diameter of the axonal ER is notably narrow, averaging approximately 40 nm, whereas the diameter ranges from 25 to 90 nm in other cell types[22]. This thin and elongated morphology makes the axonal ER susceptible to internal and external stimuli perturbations.

The tubular ER is dynamic and characterized by high membrane curvature in cross-section, with tubules undergoing continuous fusion and fission to generate and eliminate three-way junctions[23]. Two families of curvature-stabile proteins shape ER tubules, reticulons (RTNs) that comprise four reticulons in mammals (RTN1-4)[24], and DP1 that includes six mammalian DP1/ receptor accessory proteins (REEPs)[25]. Members of both families are ubiquitously expressed in all eukaryotes and localize predominantly to the tubular ER, where they have a conserved domain containing two long hydrophobic segments that sit in the membrane as hairpins[26]. These hairpins may stabilize the high curvature of tubules in cross-section by forming a wedge in the lipid bilayer[26].

There are further factors that regulate ER tubule shape. Atlastins (ATLs), a family of GTPases, mediate fusion between ER membranes in a GTP-dependent manner[27,28]. The small ras-related GTP-binding protein 10 (Rab10) and Rab18 regulate tubular ER morphology[29]. Deletion of Rab10 produces expansion of cisternal ER and fewer ER tubules, and loss of Rab18 causes fragmentation of the tubular ER and spread of ER sheets[29,30]. Lunapark is a protein that shapes the ER tubular network by stabilizing three-way junctions between ER tubules[31]. Other tubular ER regulatory proteins include ADP ribosylation factor-like 6

interacting protein 1 (ARL6IP1) and protrudin, which are found in tubular ER and possess hairpin domains determining their role in shaping the tubular ER like RTNs and REEPs[32,33]. Multiple C2 domains consist of transmembrane proteins (MCTP1 and MCTP2), which contain a reticulon homology domain. Like RTNs, these proteins tubulate the ER membrane and favor highly curved regions of the ER[34].

The biological function and regulation of axonal tubular ER

In neurons, the somatodendritic ER is an important biosynthetic site. Therefore, neuronal components such as lipids and transmembrane or secreted proteins may originate in the soma and migrate to the axons via rapid vesicular transport[35,36]. However, timely delivery of components may be difficult in neuronal compartments, particularly in the presence of fast metabolic demands during axonal development, plasticity, or regeneration. This is especially the case if the compartments are very large. Thus, the local synthesis of lipids and secreted and transmembrane proteins may support axons' remarkable extension and complexity. Remarkable progress has been achieved in the evolution of molecular markers, mastery of EM staining techniques, and determination of models for axonal ER network proteins. These advancements have unveiled the crucial involvement of numerous proteins in shaping and maintaining the structural integrity and continuous functioning of the axonal ER[37]. These findings suggest the roles in axonal ER function and the progression of neurological disorders. In human neurons, axonal ER is the potential player in the processes along axons for transporting physical cargoes[38], lipid biosynthesis, glucose homeostasis, Ca^{2+} storage, protein export, and contacting and regulating other organelles. ER contains a variety of conserved proteins that specialize in regulating particular features of its morphology. The majority of an axonal ER molecule is made up of tubular ER. Consequently, to understand the biology of the axonal ER, it is essential to understand the regulation of the tubular ER network. Table 1 summarizes the axonal tubular ER functional proteins. ER, tubules network keeps relative dynamics in the cell for communications and substance exchange.

Microtubules (MTs) are involved in driving ER tubule movement, depending on two mechanisms[39] [Figure 1]. One is mediated by the tip attachment complex (TAC)[40,41]; in TAC, the tip of an ER tubule is attached to the (+) tip of the MTs through the complex composed of the ER protein stromal interaction molecule 1 and the MTs-associated protein end-binding 1 (EB1)[42]. This binding facilitates the ER tubule movement when MTs grow or retract. Another is the "ER sliding" effect driven by MTs motor proteins, including kinesin-1 and dynein[43,44]. This process is faster and more frequent than TAC-mediated ER tubule movement[44]. Knockdown of EB1 and EB3 in neurons has been shown to reduce dendritic ER expansion without affecting axonal ER distribution[39]. Additionally, the knockdown of kinesin-1 or dynein disrupts anterograde or retrograde transport of ER tubules along the axon, supporting a critical role for ER sliding in axonal ER transport[39]. Several integral ER membrane proteins can bind MTs as potential adapters that facilitate axonal tubular ER movement, including P180 protein, also known as ribosome binding protein 1 homolog 180-kDa[45], Sec61, REEP1, and spastins (SPASTs)[46,47]. Nevertheless, the potential roles of these ER proteins in axonal ER transport remain to be explored. The ER network requires a regulated system to remove excessive ER expansion to maintain ER homeostasis. ER, autophagy (ER-phagy) allows the turnover and clearance of ER mediated by integral ER proteins, which act as ER-phagy receptors, targeting ER fragments to autophagosomes for lysosomal degradation[48-50]. The molecule identified as the tubular ER-phagy receptor is a tubular ER-shaping protein. The long N-terminal region of RTN3 contains several newly identified microtubule-associated protein 1 light chain 3 (LC3)-interacting regions that can promote the degradation of ER tubules[51]. Atlastin GTPase 3 (ATL3), a dynamin-like GTPase commonly believed to promote tubular ER fusion, also functions as an ER-phagy receptor to mediate ER tubule degradation[52]. Recently, the predicted single-pass transmembrane ER protein, testis expressed 264 (TEX264), was identified as an ER-phagy receptor, specifically mediating the degradation of ER tubule three-way junctions[53,54]. These ER-phagy receptors have been studied in non-neuronal mammalian cells, and their

Table 1. The roles of axon-resident tubular ER proteins

Proteins	Roles in tubular ER	Roles in axons
RTNs	Tubular ER-shaping protein shape ER tube formation[26]. RTN3 is a receptor for the turnover of ER tubules via ER-phagy[51]	Inhibition of axonal growth[134]; Involved in regulating levels of neurotransmission[56]; Effect in axonal development[55]; Contribute to the axonal degeneration[114]; As an ER-phage receptor contributing to the axonal ER turnover[51,135]; Involved in axonal transport[136], and axonal regeneration[137]; Promote the formation of dystrophic neurites[66]
REEPs	Tubular ER-shaping and curvature-stabilizing proteins shape ER tube formation[25,26]. Coordinate MT interactions with the tubular ER network[46,138]	Shaping and continuity of axonal ER[37]; Contribute to axonal degeneration[114], and mutations of REEP1 lead to hereditary spastic paraplegias (HSPs)[139]
ATLs	Homotypic membrane fusion between ER tubules[28,140]. Coordinate MT interactions with the tubular ER network[46,100]. ATL3 is a receptor for the turnover of ER tubules via ER-phagy[52]	Regulate morphology and function of endoplasmic reticulum in dendrites[141]; Regulate dendritic morphogenesis[27]; Promote axon regeneration[142]; Contribute to axonal degeneration, are responsible for HSP cases, account for up to 50% of all HSP cases[139,143]; Affect ER-mitochondria contact sites and axonal mitochondrial distribution[144]; Contribute distribution of presynaptic components and mobilization of synaptic vesicles[143]
Lunapark	As a curvature-stabilizing protein within tubular three-way junctions of the tubular ER[145,146]	Present in neurite-like processes[147]
RAB10	Tubular ER network organization[29]	Contributes to the axonal development[148]; Promotes axonal membrane trafficking with Lgl1 underlying neuronal polarization[149]; Regulates neurite outgrowth[150]
RAB18	Tubular ER network organization[30]	Contributes to sensory axonal degeneration[151]; Involved in neurite growth[152]
MCTPs (MCTP1, MCTP2)	ER membrane tubulating proteins tubulate the ER membrane, favor highly curved ER regions, and generally link tubular ER to organelle contact sites[34]	Function as ER-localized calcium sensor, regulate presynaptic calcium influx to stabilize baseline transmission, short-term release dynamics, and presynaptic homeostatic plasticity[153]
VAPA/B	Regulate the morphogenesis and dynamics of the tubular ER network[154,155]	Regulate synaptic activity as ER-mitochondria contacts protein[156] S
Stromal interaction molecule 1	MT-mediated transport of ER tubules by interacting with EB1[42]; Required for Remodeling of tubular ER[157]	Plays a role in midline axon guidance of commissural interneurons[158]; Contributes to synaptic function and neurite development[159]; affects axonal development[160,161]
P180	MT stabilization[39]	Controls axon specification by regulating local MTs remodeling[39]
Sec61β	Interacts with MT to maintain ER homeostasis[162]	Distributes in dendrites and axons, directly interacts with MTs, and may play a role in locally immobilizing the ER to drive efficient protein synthesis[162]
SPAST	Regulates MT-severing and tubular ER-morphogenesis[108] Regulates axonal MT stability[46,163]	Promotes axonal regeneration[142]; Contributes to degeneration of corticospinal tract axons, mutations of SPAST account for up to 50% of all HSP cases[139]; Involved in axonal swellings and axonal transport[105,106]
TEX264	As a receptor for the turnover of ER tubules via ER-phagy[53,54]	Unknown

roles in neurons remain to be explored. Notably, RTN3 is highly expressed in the brain and is essential in axonal development[55]. Recent studies demonstrated that RTN3 overexpression causes the clustering of the tubular ER in the dystrophic neurites of axons and dendrites in the hippocampus from amyloid precursor protein (APP) mice[12] and AD patients[12]. The underlying mechanisms remain unclear. However, a recent study suggests that autophagy is involved in the tubular ER accumulation in axons of hippocampal neurons[56], suggesting that autophagy deficits may accelerate tubular ER accumulation in axons.

Studies of the relationship between autophagy and tubular ER showed that ATL3 Y192C mutation resulted in axon growth deficits by reducing autophagy and the number of ER exit sites[57]. Autophagy and the tubular ER were detected in the early stage during dystrophic neurite (DN) growth in AD models[58]. RTN3 and the pre-autophagosome protein ATG9A enriched DNs when plaques began to develop, and LC3 appeared in DNs at later stages, proving that DNs evolve from dysfunctional pre-autophagosomes, tubular ER, and mature autophagosomes[58]. Although these studies determine the relationship between autophagy and tubular ER in axons, much remains unknown about how autophagy regulates tubular ER in axonal degeneration and whether autophagy modulation could be a potential therapeutic strategy for tubular ER-

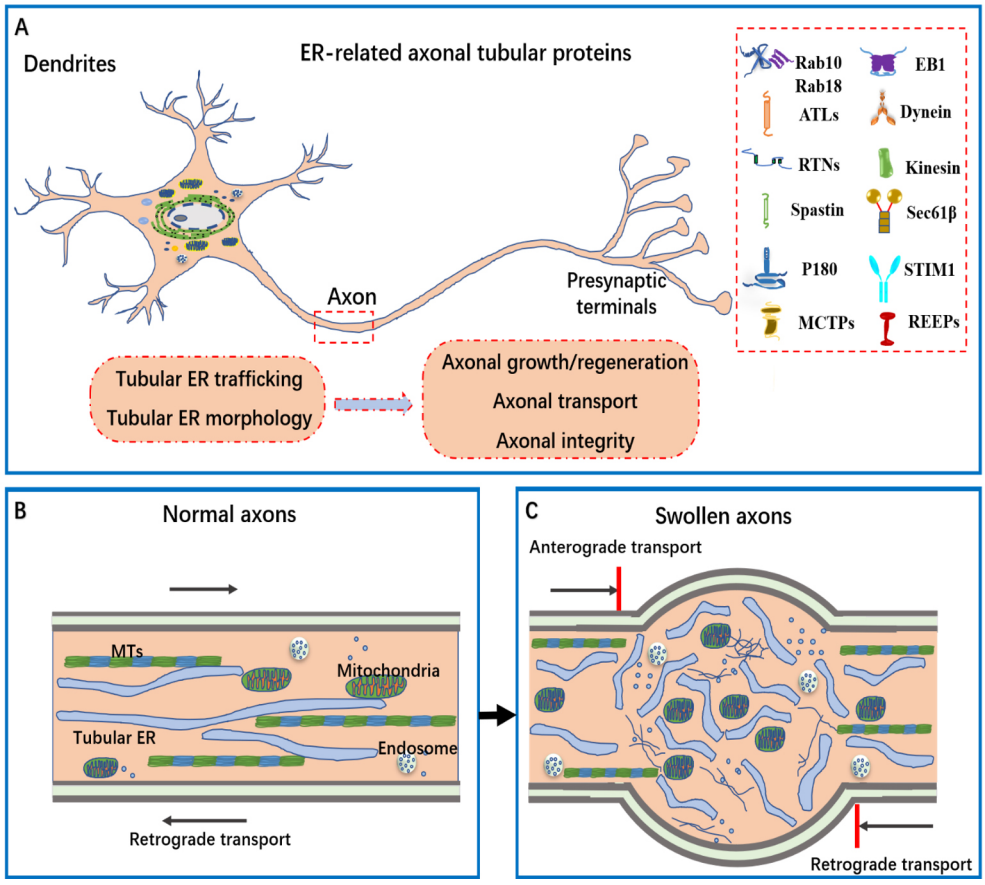

Figure 1. Influence of the axonal ER morphology and dynamics on healthy and pathological axons. A: Factors important in the morphogenesis process and the dynamics of ER-related axonal tubular function [See Table 1 and Figure 2]; B: The axonal ER in a normal cell is active, exhibiting normal anterograde and retrograde trafficking; C:However, when tubular ER protein aggregates and other organelles accumulate in the axons under certain conditions (like gene mutation or failed clearance), leading to axonal deformation, there are axonal transport abnormalities; ER: Endoplasmic reticulum; Rab10,18: ras-related GTP-binding protein 10,18; EB1: End-binding 1; STIM1: Stromal interaction molecule 1; REEPs: Receptor accessory proteins; ATL: Atlastin; RTNs: Reticulons; P180: Protein 180; MTs: Microtubules.

related dysfunction in neurodegenerative disorders.

THE CONTRIBUTION OF TUBULAR ER IN THE AXONAL DEGENERATION OF NEURODEGENERATIVE DISORDERS

The process of axonal degradation, which takes place in the early stages of neurodegenerative illnesses, nevertheless occurs as a natural consequence of aging. Several age-related alterations in cellular mechanisms have been found to contribute to axonal degeneration. A growing body of evidence suggests a close association between axonal tubular ER and various neurodegenerative disorders; nevertheless, the underlying pathogenic processes and molecular mechanisms of tubular ER in the axonal degeneration of neurodegenerative disorders have not been fully understood. Although the molecular basis leading an individual to develop the neurodegenerative disorder is largely unknown, the growing body of evidence supports the important role of axonal degeneration and ER proteostasis impairment in the pathophysiology of those disorders.

Tubular ER dysfunction and axonal degeneration in AD

AD is a neurodegenerative disorder with insidious onset and slow progression, causing a decline in memory and difficulties in speaking, writing, understanding, identifying objects, and disorientation. The neuropathological hallmarks of the AD brain are diffuse and neuritic extracellular amyloid plaques, which are commonly surrounded by DNs and intracellular neurofibrillary tangles[59]. Mutations in APP and in the proteases that create beta-amyloid from APP, Presenilin-1, and-2 can cause early-onset AD. Apolipoprotein E/E4, a protein implicated in lipid metabolism and inflammation, is a substantial genetic risk factor for late-onset AD. APP is a transmembrane protein folded and processed in the ER before being transported to the outer membrane via the Golgi apparatus[60,61]. Dysfunctional tubular ER in DNs is a feature of AD pathogenesis. DNs are swollen dendrites or axons recognizable near amyloid plaques as an early event of AD[62,63]; they represent axonal structures with cytoskeletal abnormalities in AD patients and AD models. In preclinical AD cases, DNs contain neurofilament (NF) triplet proteins, phospho-APP (T668), and α-internexin, but not phosphorylated tau[64]. In contrast, DNs in AD cases are labeled with phosphorylated tau[65]. Thus, the biochemical properties of DNs reflect disease progression.

Over the past two decades, many genetic and biochemical studies have revealed various molecular mechanisms contributing to the pathology of DNs. Even though proteins such as APP, neurofilament, ubiquitin, α-internexin, and GAP-43 were reported to label DNs in areas surrounding amyloid plaques in AD brains[63], tubular ER recently has come to the attention of researchers because it actively participates in forming DNs and participates in AD pathophysiology[12,66].

Recent studies have shown that the tubular ER actively forms DNs and contributes to AD pathophysiology. Specifically, Hu first found the formation of high molecular-weight RTN3 aggregates near the amyloid plaques in brains of AD cases and mice expressing mutant AP, and overexpressing RTN3 can induce DNs in the hippocampus, accompanied by impaired learning and memory and synaptic plasticity in mice[66]. Moreover, the tubular ER was fragmented and accumulated in the axonal terminals of the brains of AD patients and AD mouse models[12]. However, only RTN3, but not other members of the RTNs family, accumulate in the DNs[12], which may be associated with the RTN3 mediate-tubular ER trafficking in axons by interacting with dynactin 6, a protein involved in dynein-mediated retrograde transport of cargo vesicles[67].

RTN3 is most often studied in the association of tubular ER and AD pathology, and other genes associated with tubular ER have been identified that participate in AD pathological progression. REEP2 and REEP5 colocalized with DNs[12]. Protein 600 (p600) colocalized with mitochondria and the ER marker Bip in a vesicular or punctate pattern in primary mouse cortical neurons. Silencing of p600 destabilized neuronal processes in young primary neurons undergoing neurite extension and contained scarce staining of the ER marker Bip. Disruption of the neuronal tubular ER and mitochondria interaction may impact cellular processes, including neuronal maturation and axonal transport[68]. RAB10 is found to have a role in AD, and its expression is significantly elevated in the human AD brain[69]. Rab10 knockdown leads to a significant decrease in amyloid β 42 (Aβ42) and Aβ42/Aβ40 ratio[70]. ER dynamics and morphology control tubulation along MTs and tubule fusion[29]. Functional categorization of the list of proteins, enriched explicitly in ER tubules, reveals that the tubular ER network is involved in membrane trafficking, organelle contact, and stress sensing in *Saccharomyces cerevisiae*[11,71], which supports the notion that the ER tubules are broadly involved in lipid metabolism[71]. Mammalian serine palmitoyltransferase (SPT) regulates ceramide levels that directly mediate Aβ levels, and inhibition of serine SPT reduces Aβ and tau hyperphosphorylation in an AD mouse model, providing a potential therapeutic strategy for AD[72]. Activated astrocytes via serine palmitoyltransferase increase BACE1 in primary neurons, contributing to AD progress[73]. It is believed that tubular ER proteins contribute to AD pathogenesis by regulating lipid metabolism, forming DNs, and

interacting with other cellular components, including mitochondria. Identifying these proteins provides new targets for developing therapeutic strategies for AD.

Tubular ER degeneration in PD

PD is the second most common neurodegenerative disease after AD. The movement disorder is caused by the loss of dopaminergic neurons in the substantia nigra pars compacta, with intracellular aggregation of α-synuclein in Lewy bodies (LBs) and Lewy neurites (LNs)[74]. LBs are protein inclusions containing disaggregated oligomers of many cellular proteins, and LNs are precursors of LBs with deposits of ubiquitin and α-synuclein and possibly other molecules that accumulate in synaptic terminals and axonal processes and linked to neuroinflammation and synucleinopathies[75,76]. Autophagosome-like membranes were observed in globules, small axonal swellings derived from the PD mouse model expressing human wild-type α-synuclein or β-synuclein[7], suggesting that autophagy contributes to LN formation.

α-Synuclein neurotoxicity has been linked to impairments in various cellular functioning features, including mitochondrial, proteasomal, and lysosomal abnormalities, axonal transport deficits, and synaptic transmission changes[77]. ER, stress has recently emerged as a mediator of α-synuclein toxicity[78]. In addition, the dominant family variants of PD are caused by mutations in α-synuclein which disrupts ER-mitochondria tethering by binding to vesicle-associated membrane-protein-associated protein B (VAPB)[79,80]. Furthermore, VAPB has altered binding to protein tyrosine phosphatase interacting protein-51 and increases Ca^{2+} uptake by mitochondria following release from ER stores[79]. Also, the Ca^{2+} homeostasis is one of the primary functions of the tubular ER. A PINK1 mutation causes mitochondrial abnormalities such as loss of membrane potential, increased size, and decreased ATP levels, all of which are reversed in PD cell models by inhibiting mitochondrial calcium uniporters, which take up Ca^{2+} released from the ER[81]. These findings suggest that ER-mitochondria interactions may influence the severity of PD symptoms.

The *MCTP2* gene, a human homolog of Pex30 with N-terminal reticulon homology domain and putative functions in tubular ER formation, has been identified as a risk factor for developing early-onset PD49[34,82], suggesting that ER organization disruption in dopaminergic axons might accelerate PD development. In addition, increases in ER-mitochondria contact sites generate abnormal lipid trafficking, which depletes phosphatidylserine from ER in *Drosophila* and PD cell models. This ER lipid abnormality disrupts sleep patterns[83], the common non-motor manifestation of PD. It is known that PD links to impairments in various cellular functions, including mitochondrial, proteasomal, and lysosomal abnormalities, ER stress, and ER-mitochondria tethering disruption. The importance of Tubular ER degeneration in PD could help understand the role of tubular ER and its interactions in PD pathology and develop targeted therapies that can prevent or slow disease progression.

Tubular ER degeneration in ALS

ALS is a fatal neurodegenerative disease caused by gradually deteriorating upper and lower motor neurons[84]. In ALS, neurodegeneration is characterized by distal axonopathy that begins at the distal axons, including the neuromuscular junctions, and progresses proximally in a "dying back" manner prior to the degeneration of cell bodies[85]. However, the molecular mechanism for distal axonopathy in ALS has not been fully elucidated. A toxic gain of function caused by aberrant protein aggregation in axons is likely one of the major drivers of axonopathy[86]. Spheroids are found in proximal axons of motor neurons of lumbar spinal cords in ALS patients but are not specific to ALS, and small numbers of spheroids may also appear with increasing age in healthy elderly individuals and non-ALS neurological patients[85]. However, axonal spheroids with accumulated some aberrant protein aggregations, such as phosphorylated neurofilaments[87], and phosphorylated TAR DNA binding protein 43[88], were specific to ALS patients but not to disease controls.

Several lines of evidence suggest that RTNs, particularly members of the neuronal surface glycosylphosphatidylinositol-linked receptor (Nogo) (also called RTN4) subfamily, are involved in ALS pathogenesis[89]. Nogo isoforms, especially Nogo-A, are expressed in the skeletal muscles and brains of ALS mouse models and patients, and their levels correlate with the disease severity[90]. Nogo-A overexpression destabilizes neuromuscular junctions, which may cause terminal nerve retraction and denervation with motor neuron death and muscle atrophy[89,91]. Nogo inhibits the axonal outgrowth and regeneration in the central nervous system via the Nogo-A receptor (NgR)[92]. Ablation of Nogo delays disease progression in the SOD1 ^{G93A} mouse model of ALS[93], and targeting NgR can reduce ALS protein ataxin-2[94], suggesting that pharmacological inhibition of Nogo-A or NgR may be a disease-modifying approach in ALS. Nogo-A expression may be a helpful biomarker for identifying ALS in the early stages when the diagnosis is difficult to confirm. Increased Nogo-A mRNA is found in the transgenic ALS model at early asymptomatic stages, while Nogo-A levels are barely detectable in healthy adult muscles[95]. Muscle Nogo-A expression could be a prognostic marker in the lower motor neuron syndrome (LMNS), considered the initial stage of ALS.

Enhanced Nogo-A expression in biopsy samples from patients with LMNS allows for identifying patients at higher risk of progressing to ALS[96]. Nogo-A may be an early indicator of the disease and an adverse prognostic factor in patients with ALS, for ALS-related denervation was excluded in Nogo-A-negative patients. VAPA/VAPB participates in mitochondrial-associated membranes, and dysfunction could disturb ER membrane trafficking and promote axonal degeneration. A point mutation (P56S) in the VAPB leads to an autosomal dominant form of ALS, involved with ER-associated aggregates that completely reorganize ER structures[97]. ALS-related protein at Ataxin-2 may also contribute to the ALS process by stabilizing MT and actin networks and maintaining tubular ER morphogenesis and dynamics[98,99].

Tubular ER in HSPs neural degeneration

HSPs are a group of neurodegenerative disorders caused by the degeneration of upper motor neurons and their axons in the longest corticospinal tract. They are divided into pure and complex forms, with spasticity in lower limbs only, or associated with other neurologic and non-neurologic manifestations, respectively[100]. Clinically, patients display lower limb weakness, spasticity, and bladder dysfunction[101]. With 87 forms described, they are a significant health and economic problem for society and patients[102]. One of the pathogenic mechanisms underlying HSPs appears to be axonal degeneration[103,104]. Defective cellular membrane trafficking (and, more specifically, impaired axonal transport of macromolecules and organelles) is the genetic mechanism of HSP that has received the most attention and research. Approximately 50% of those diagnosed with HSP harbor mutations in tubular ER proteins, including MT-severing ATPase SPAST, the membrane-bound GTPase ATL1, RTN-like, and MT-binding protein REEP1. Transverse ER expansion was found in corticospinal axons of HSP mice[100], suggesting a possible connection between tubular ER modeling and axon integrity. SPAST, ATL1, and REEP1 interact within the tubular ER membrane in corticospinal neurons to coordinate ER shaping and MT dynamics. Defects in tubular ER shaping and network interactions with the axonal MT cytoskeleton seem to be the predominant pathogenic mechanism of HSP[46].

Autosomal dominant mutations in the *SPAST* gene cause spastic paraplegia 4 (SPG4), the most common form of pure HSP. Pathological analysis of human SPG4 cases reveals the presence of largely axonal swellings, also observed in a mouse model with pathogenic splice site mutation of *SPAST*[105]. *SPAST* mutation significantly impacts axons in cell and mouse models, illustrating swollen axons with an accumulation of acetyl-α-tubulin, tau, cytoskeletal proteins, and APP[106]. These findings suggest that the component of axonal swellings may be associated with deficits in axonal transport.

Poor transportation leads to materials building up in axons and their deformation. The observation supports the notion that these swellings of axons are linked to axonal MT dynamics[106]. Because of the essential role of MT in axonal transport, defects in axonal transport may underlie at least part of the disease process in HSPs[105]. Mitochondrial transport in axons was decreased in SPG4 neurons. Furthermore, the mitochondrial axonal transport defects are exacerbated in neurons with axonal swellings, and anterograde and retrograde transport between axonal swellings or terminals to axonal swellings were severely reduced[107]. The lack of SPAST enlarges the axonal ER and reduces store-operated calcium entry, leading to abnormal Ca^{2+} homeostasis[108], which may serve as a disease-relevant mechanism of SPAST-linked motor neuron disease.

Interestingly, studies using transgenic mice with human mutant *SPAST* gene (hSPAST-C448Y) have shown that these animals develop corticospinal dieback and gait deficits but not axonal swellings[109]. However, in *SPAST* knockout mice, axonal swellings are observed, but they neither display dieback degeneration nor gait deficiencies[105,106,110]. A debate has arisen in the field of HSPs regarding whether axonal swellings caused by reduced SPAST function are the primary cause of the disease or merely exacerbate the toxic effects of the mutant protein. A recent study shed light on this issue by crossbreeding *SPAST* knockout mice with transgenic mice carrying hSPAST-C448Y[111]. The study found that the crossbred animals exhibited earlier symptoms, worsened gait deficiencies, and corticospinal dieback compared to the hSPAST-C448Y mouse. These results suggest that reduced spastin function does not appear to be the primary cause of HSPs but contributes to the disease's pathogenesis by exacerbating the toxic effects of the mutant protein. The model also provides a more accurate representation of the disease's complexity and enables researchers to investigate the molecular mechanisms underlying the disease[111]. Although the exact role of SPAST in axonal swellings is not yet fully understood, the above finding provides new insights into future research to understand the pathogenesis of HSPs. Recently, additional mutations have been identified in HSPs. REEP1 mutations have been found to cause axonal degeneration[112,113]. Furthermore, using advanced genetic sequencing techniques, three mutations in the RTN2 gene were discovered in families with SPG12[114]. Mutated RTN2 links ER shaping with axonopathy, supporting the hypothesis that abnormal ER morphogenesis is a pathogenic mechanism in HSPs[114]. ARL6IP1 is an ER-localized anti-apoptotic regulator and a potential factor in structuring the ER tubules in mammalian cells. It has been associated with regulating glutamate in neurons[115]. When the gene is knocked down in Drosophila, the result is a progressive motor deficit[116]. Novarino *et al.* performed whole exome sequencing and found a homozygous loss-of-function mutation in ARL6IP1 in a family with SPG61[117]. Some ER-shaping proteins associated with HSPs have functions in other cellular processes, including lipid metabolism[118], Ca^{2+} signaling[119], and mitochondrial regulation[116], which may contribute to the disease process. We believe that mutations in genes associated with HSPs can lead to an abnormal expansion of the tubular ER in axons, resulting in axonal degeneration. This is due to an imbalance in the regulation of the tubular ER membrane, which leads to excessive membrane expansion and a loss of membrane integrity. Further study of how targeting the regulation of the tubular ER membrane could be a potential therapeutic strategy for treating HSPs is needed to understand the pathogenesis of HSPs and develop targeted treatments.

Tubular ER degeneration in HD

HD is a progressive disorder inherited in an autosomal dominant pattern responsible for many motor, mental, and cognitive symptoms[120]. HD is a monogenic disorder caused by an expansion of CAG trinucleotide repeats in exon 1 of the HTT gene (also known as the IT15 gene), which encodes the 348 kDa huntingtin protein (HTT)[121]. HTT expansions have been linked to abnormalities in anterograde and retrograde transport of vesicles carrying growth factors, including brain-derived neurotrophic factors[122]. HTT aggregates have been shown in *Drosophila* and mouse models to be directly neurotoxic by affecting axonal transport[123,124]. Another study found that HTT modulates axonal transport by sequestering motor

proteins into aggregates, based on the finding that the pool of soluble motors reduces when polyQ HTT repeats are expressed[123]. Overall, the findings in HD show that protein aggregation can be a source of axonal transport abnormalities.

Ca^{2+} signaling is disrupted in HD disease models[125], implying that disturbed Ca^{2+} handling makes spiny projection neurons more sensitive to Ca^{2+}-mediated cell death. The binding of HTT to inositol 1,4,5-trisphosphate (IP3R) improves receptor responsiveness to IP3, leading to increased Ca^{2+} release[126], which may eventually lead to apoptosis. The increased Ca^{2+} leak also depletes ER Ca^{2+} reserves, inducing store-operated channel ER Ca^{2+} replenishment[125]. This interaction between HTT and IP3R could result in neurodegeneration. IP3R blockers prevent increased glutamate-mediated cell death in mouse striatal neurons[127,128] and mouse neuronal cell cultures. A repeat expansion in the *Junctophilin 3* gene also interacts with HD-like 2[129], which phenocopies HD. Junctophilin 3 stimulates ER-plasma membrane contact sites, which regulate Ca^{2+} communication in hippocampus neurons[130]. The chorea-acanthocytosis, which has a phenotype similar to HD, is caused by mutations in the gene Vps13A[131]. Vps13A is a lipid-transfer protein identified at ER-membrane contact sites with mitochondria and LDs; it also facilitates ER-membrane contact sites tethering[132,133]; thus, Vps13A dysfunction could impact Ca^{2+} communication. These findings suggest ER participation in Ca^{2+} handling is critical for HD pathogenesis and may represent therapeutic targets.

CONCLUSION AND PERSPECTIVES

Axonal tubular ER is a distinctive structure found in neuron axons. Its tubular form allows it to regulate various biological processes important for axonal function and neural transmission. Axonal tubular ER dysfunction has been linked to various neurodegenerative disorders [Figure 2], emphasizing the necessity of this structure in preserving neuronal integrity. Axonal degeneration is a pathogenic characteristic shared by many neurodegenerative disorders, and it causes a breakdown in neuronal communication. For these reasons, axonal ER dysfunction contribute to axonal degeneration, while the original cause of the axonal ER abnormality remains unclear. One consideration is structural deficits of axonal ER caused by tubular ER-shaping gene mutations because the abnormal morphology of tubular ER is incompetent to maintain normal function. Another consideration is related to MTs dysfunction because the normal axonal transport function depends on the cooperation of tubular ER and MTs, of which MTs deficits also lead to the failed transport of axonal materials, causing further axonal deformation and degeneration. The third consideration includes cargo clearance in axons, which recapitulates the process of autophagy. ER-phagy is the predominant pathway for axonal ER turnover; any disturbance, such as aging or toxic factors, attenuates or damages cellular autophagy. Although the tubular ER overlap in the axonal degeneration of neurodegenerative disorders with genetic and biological factors likely to play roles in the clinical manifestations of axonal degeneration-associated disorders, the relationship requires further study. Determining the primary cellular defects and correlating the consequences with the ER tubular changes that may appear at different disease stages is crucial to help define the pathogenesis of those neurodegenerative disorders. Furthermore, it will be vital to design effective future therapies that specifically counteract the causes of tubular ER and axonal degeneration-associated disorders.

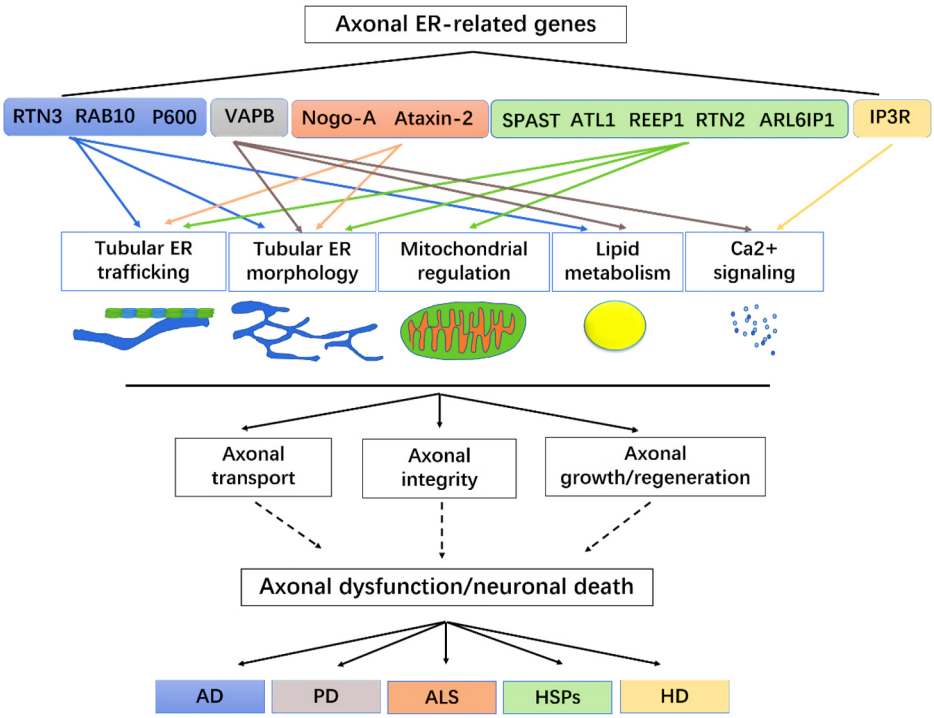

Figure 2. The putative tubular ER neurodegenerative mechanism. This figure illustrates the complex interplay of the main mechanisms involved in axonal tubular ER pathology in neurodegenerative disorders. Arrows show the regulation of the specified process. The dashed arrows indicate the consequences of interrupting the corresponding process; ER: Endoplasmic reticulum; RTN3: Reticulons3; Rab10: ras-related GTP-binding protein 10; p600: Protein 600; VAPB: Vesicle-associated membrane-protein-associated protein B; Nogo-A: Neuronal surface glycosylphosphatidylinositol-linked receptor-A; SPAST: Spastin; ATL: Atlastin; REEP1: Receptor accessory proteins1; IP3R: Inositol 1,4,5-trisphosphate; ARL6IP1: ADP ribosylation factor-like 6 interacting protein; AD: Alzheimer's disease; PD: Parkinson's disease; ALS: Amyotrophic lateral sclerosis; HSPs: Hereditary spastic paraplegias; HD: Huntington's disease.

DECLARATIONS

Author contributions

Performed the literature search and wrote the manuscript: Wang PP, Al-Nusaif M Initiated the concept, gave administrative supervision, and helped edit this manuscript: Le WD

Read and agreed to the published version of the manuscript: Wang PP, Al-Nusaif M, Le WD

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Adalbert R, Nogradi A, Babetto E, et al. Severely dystrophic axons at amyloid plaques remain continuous and connected to viable cell bodies. *Brain* 2009;132:402-16. DOI
2. Orimo S, Amino T, Itoh Y, et al. Cardiac sympathetic denervation precedes neuronal loss in the sympathetic ganglia in Lewy body disease. *Acta Neuropathol* 2005;109:583-8. DOI
3. Ferraiuolo L, Kirby J, Grierson AJ, Sendtner M, Shaw PJ. Molecular pathways of motor neuron injury in amyotrophic lateral sclerosis. *Nat Rev Neurol* 2011;7:616-30. DOI PubMed
4. Coleman M. Axon degeneration mechanisms: commonality amid diversity. *Nat Rev Neurosci* 2005;6:889-98. DOI PubMed
5. Palumbo A, Grüning P, Landt SK, et al. Deep learning to decipher the progression and morphology of axonal degeneration. *Cells* 2021;10:2539. DOI PubMed PMC
6. Lomoio S, Willen R, Kim W, et al. Gga3 deletion and a GGA3 rare variant associated with late onset Alzheimer's disease trigger BACE1 accumulation in axonal swellings. *Sci Transl Med* 2020:12. DOI PubMed PMC
7. Sekigawa A, Takamatsu Y, Sekiyama K, Hashimoto M. Role of α- and β-synucleins in the axonal pathology of parkinson's disease and related synucleinopathies. *Biomolecules* 2015;5:1000-11. DOI PubMed PMC
8. Kobayakawa Y, Sakumi K, Kajitani K, et al. Galectin-1 deficiency improves axonal swelling of motor neurones in SOD1(G93A) transgenic mice. *Neuropathol Appl Neurobiol* 2015;41:227-44. DOI PubMed
9. Galvin JE, Uryu K, Lee VM, Trojanowski JQ. Axon pathology in Parkinson's disease and Lewy body dementia hippocampus contains alpha-, beta-, and gamma-synuclein. *Proc Natl Acad Sci U S A* 1999;96:13450-5. DOI PubMed PMC
10. Kuijpers M, Kochlamazashvili G, Stumpf A, et al. Neuronal autophagy regulates presynaptic neurotransmission by controlling the axonal endoplasmic reticulum. *Neuron* 2022;110:734. DOI PubMed PMC
11. Öztürk Z, O'Kane CJ, Pérez-Moreno JJ. Axonal endoplasmic reticulum dynamics and its roles in neurodegeneration. *Front Neurosci* 2020;14:48. DOI PubMed PMC
12. Sharoar MG, Shi Q, Ge Y, et al. Dysfunctional tubular endoplasmic reticulum constitutes a pathological feature of Alzheimer's disease. *Mol Psychiatry* 2016;21:1263-71. DOI PubMed PMC
13. Westrate LM, Lee JE, Prinz WA, Voeltz GK. Form follows function: the importance of endoplasmic reticulum shape. *Annu Rev Biochem* 2015;84:791-811. DOI PubMed
14. Luarte A, Cornejo VH, Bertin F, Gallardo J, Couve A. The axonal endoplasmic reticulum: one organelle-many functions in development, maintenance, and plasticity. *Dev Neurobiol* 2018;78:181-208. DOI PubMed
15. Shibata Y, Shemesh T, Prinz WA, et al. Mechanisms determining the morphology of the peripheral ER. *Cell* 2010;143:774-88. DOI PubMed PMC
16. Baumann O, Walz B. Endoplasmic reticulum of animal cells and its organization into structural and functional domains. Elsevier; 2001. pp. 149-214. DOI
17. Lin S, Meng T, Huang H, et al. Molecular machineries and physiological relevance of ER-mediated membrane contacts. *Theranostics* 2021;11:974-95. DOI PubMed PMC
18. Terasaki M, Slater NT, Fein A, Schmidek A, Reese TS. Continuous network of endoplasmic reticulum in cerebellar Purkinje neurons. *Proc Natl Acad Sci USA* 1994;91:7510-4. DOI PubMed PMC
19. Wu Y, Whiteus C, Xu CS, et al. Contacts between the endoplasmic reticulum and other membranes in neurons. *Proc Natl Acad Sci U S A* 2017;114:E4859-67. DOI PubMed PMC
20. Horton AC, Ehlers MD. Neuronal polarity and trafficking. *Neuron* 2003;40:277-95. DOI PubMed
21. Shibata Y, Voeltz GK, Rapoport TA. Rough sheets and smooth tubules. *Cell* 2006;126:435-9. DOI PubMed
22. Terasaki M. Axonal endoplasmic reticulum is very narrow. *J Cell Sci* 2018;131:jcs210450. DOI PubMed
23. Terasaki M, Shemesh T, Kasthuri N, et al. Stacked endoplasmic reticulum sheets are connected by helicoidal membrane motifs. *Cell* 2013;154:285-96. DOI PubMed PMC
24. Oertle T, Klinger M, Stuermer CA, Schwab ME. A reticular rhapsody: phylogenic evolution and nomenclature of the RTN/Nogo gene family. *FASEB J* 2003;17:1238-47. DOI PubMed
25. Powers RE, Wang S, Liu TY, Rapoport TA. Reconstitution of the tubular endoplasmic reticulum network with purified components. *Nature* 2017;543:257-60. DOI PubMed PMC
26. Voeltz GK, Prinz WA, Shibata Y, Rist JM, Rapoport TA. A class of membrane proteins shaping the tubular endoplasmic reticulum. *Cell* 2006;124:573-86. DOI PubMed
27. Gao Y, Jiang T, Qu C, et al. Atlastin-1 regulates dendritic morphogenesis in mouse cerebral cortex. *Neurosci Res* 2013;77:137-42. DOI

28. Orso G, Pendin D, Liu S, et al. Homotypic fusion of ER membranes requires the dynamin-like GTPase atlastin. *Nature* 2009;460:978-83. DOI
29. English AR, Voeltz GK. Rab10 GTPase regulates ER dynamics and morphology. *Nat Cell Biol* 2013;15:169-78. DOI PubMed PMC
30. Gerondopoulos A, Bastos RN, Yoshimura S, et al. Rab18 and a Rab18 GEF complex are required for normal ER structure. *J Cell Biol* 2014;205:707-20. DOI PubMed PMC
31. Chen S, Desai T, McNew JA, et al. Lunapark stabilizes nascent three-way junctions in the endoplasmic reticulum. *Proc Natl Acad Sci USA* 2015;112:418-23. DOI PubMed PMC
32. Yamamoto Y, Yoshida A, Miyazaki N, Iwasaki K, Sakisaka T. Arl6IP1 has the ability to shape the mammalian ER membrane in a reticulon-like fashion. *Biochem J* 2014;458:69-79. DOI
33. Sonda S, Pendin D, Daga A. ER morphology in the pathogenesis of hereditary spastic paraplegia. *Cells* 2021;10:2870. DOI PubMed PMC
34. Joshi AS, Ragusa JV, Prinz WA, Cohen S. Multiple C2 domain-containing transmembrane proteins promote lipid droplet biogenesis and growth at specialized endoplasmic reticulum subdomains. *Mol Biol Cell* 2021;32:1147-57. DOI PubMed PMC
35. Roy S. Seeing the unseen: the hidden world of slow axonal transport. *Neuroscientist* 2014;20:71-81. DOI PubMed PMC
36. Twelvetrees A, Hendricks AG, Holzbaur EL. SnapShot: axonal transport. *Cell* 2012;149:950-950.e1. DOI PubMed
37. Yalçın B, Zhao L, Stofanko M, et al. Modeling of axonal endoplasmic reticulum network by spastic paraplegia proteins. *Elife* 2017;6:e23882. DOI PubMed PMC
38. Millecamps S, Julien JP. Axonal transport deficits and neurodegenerative diseases. *Nat Rev Neurosci* 2013;14:161-76. DOI PubMed
39. Farías GG, Fréal A, Tortosa E, et al. Feedback-driven mechanisms between microtubules and the endoplasmic reticulum instruct neuronal polarity. *Neuron* 2019;102:184-201.e8. DOI
40. Waterman-Storer CM, Gregory J, Parsons SF, Salmon ED. Membrane/microtubule tip attachment complexes (TACs) allow the assembly dynamics of plus ends to push and pull membranes into tubulovesicular networks in interphase Xenopus egg extracts. *J Cell Biol* 1995;130:1161-9. DOI PubMed PMC
41. Waterman-Storer CM, Salmon ED. Endoplasmic reticulum membrane tubules are distributed by microtubules in living cells using three distinct mechanisms. *Curr Biol* 1998;8:798-806. DOI PubMed
42. Grigoriev I, Gouveia SM, van der Vaart B, et al. STIM1 is a MT-plus-end-tracking protein involved in remodeling of the ER. *Curr Biol* 2008;18:177-82. DOI PubMed PMC
43. Bridgman PC. Myosin Va movements in normal and dilute-lethal axons provide support for a dual filament motor complex. *J Cell Biol* 1999;146:1045-60. DOI PubMed PMC
44. Woźniak MJ, Bola B, Brownhill K, et al. Role of kinesin-1 and cytoplasmic dynein in endoplasmic reticulum movement in VERO cells. *J Cell Sci* 2009;122:1979-89. DOI PubMed PMC
45. Diefenbach RJ, Diefenbach E, Douglas MW, Cunningham AL. The ribosome receptor, p180, interacts with kinesin heavy chain, KIF5B. *Biochem Biophys Res Commun* 2004;319:987-92. DOI PubMed
46. Park SH, Zhu PP, Parker RL, Blackstone C. Hereditary spastic paraplegia proteins REEP1, spastin, and atlastin-1 coordinate microtubule interactions with the tubular ER network. *J Clin Invest* 2010;120:1097-110. DOI PubMed PMC
47. Zhu Y, Zhang G, Lin S, et al. Sec61β facilitates the maintenance of endoplasmic reticulum homeostasis by associating microtubules. *Protein Cell* 2018;9:616-28. DOI PubMed PMC
48. Hübner CA, Dikic I. ER-phagy and human diseases. *Cell Death Differ* 2020;27:833-42. DOI PubMed PMC
49. Karabiyik C, Frake RA, Park SJ, Pavel M, Rubinsztein DC. Autophagy in ageing and ageing-related neurodegenerative diseases. *AND* 2021. DOI
50. Kuo SH, Tasset I, Cuervo AM, Sulzer D. Misfolded GBA/β-glucocerebrosidase impairs ER-quality control by chaperone-mediated autophagy in Parkinson disease. *Autophagy* 2022;18:3050-2. DOI PubMed PMC
51. Grumati P, Morozzi G, Hölper S, et al. Full length RTN3 regulates turnover of tubular endoplasmic reticulum via selective autophagy. *Elife* 2017;6:e25555. DOI PubMed PMC
52. Chen Q, Xiao Y, Chai P, et al. ATL3 Is a tubular ER-phagy receptor for GABARAP-mediated selective autophagy. *Curr Biol* 2019;29:846-855.e6. DOI PubMed
53. Chino H, Hatta T, Natsume T, Mizushima N. Intrinsically disordered protein TEX264 mediates ER-phagy. *Mol Cell* 2019;74:909-921.e6. DOI PubMed
54. An H, Ordureau A, Paulo JA, et al. TEX264 Is an endoplasmic reticulum-resident ATG8-interacting protein critical for ER remodeling during nutrient stress. *Mol Cell* 2019;74:891-908.e10. DOI PubMed PMC
55. Kumamaru E, Kuo CH, Fujimoto T, et al. Reticulon3 expression in rat optic and olfactory systems. *Neurosci Lett* 2004;356:17-20. DOI
56. Kuijpers M, Kochlamazashvili G, Stumpf A, et al. Neuronal autophagy regulates presynaptic neurotransmission by controlling the axonal endoplasmic reticulum. *Neuron* 2021;109:299-313.e9. DOI PubMed PMC
57. Behrendt L, Kurth I, Kaether C. A disease causing ATLASTIN 3 mutation affects multiple endoplasmic reticulum-related pathways. *Cell Mol Life Sci* 2019;76:1433-45. DOI PubMed PMC
58. Sharoar MG, Hu X, Ma XM, Zhu X, Yan R. Sequential formation of different layers of dystrophic neurites in Alzheimer's brains. *Mol Psychiatry* 2019;24:1369-82. DOI PubMed PMC

59. Reitz C, Brayne C, Mayeux R. Epidemiology of alzheimer disease. *Nat Rev Neurol* 2011;7:137-52. DOI PubMed PMC
60. Cauwenberghe C, Van Broeckhoven C, Sleegers K. The genetic landscape of Alzheimer disease: clinical implications and perspectives. *Genet Med* 2016;18:421-30. DOI PubMed PMC
61. Kumar K, Kumar A, Keegan RM, Deshmukh R. Recent advances in the neurobiology and neuropharmacology of Alzheimer's disease. *Biomed Pharmacother* 2018;98:297-307. DOI PubMed
62. Uchida Y, Gomi F. The role of calsyntenin-3 in dystrophic neurite formation in Alzheimer's disease brain. *Geriatr Gerontol Int* 2016;16 Suppl 1:43-50. DOI PubMed
63. Blanchard V, Moussaoui S, Czech C, et al. Time sequence of maturation of dystrophic neurites associated with Abeta deposits in APP/PS1 transgenic mice. *Exp Neurol* 2003;184:247-63. DOI PubMed
64. Dickson TC, King CE, McCormack GH, Vickers JC. Neurochemical diversity of dystrophic neurites in the early and late stages of Alzheimer's disease. *Exp Neurol* 1999;156:100-10. DOI PubMed
65. Woodhouse A, Vickers JC, Adlard PA, Dickson TC. Dystrophic neurites in TgCRND8 and Tg2576 mice mimic human pathological brain aging. *Neurobiol Aging* 2009;30:864-74. DOI PubMed
66. Hu X, Shi Q, Zhou X, et al. Transgenic mice overexpressing reticulon 3 develop neuritic abnormalities. *EMBO J* 2007;26:2755-67. DOI PubMed PMC
67. Sharoar MG, Zhou J, Benoit M, He W, Yan R. Dynactin 6 deficiency enhances aging-associated dystrophic neurite formation in mouse brains. *Neurobiol Aging* 2021;107:21-9. DOI PubMed PMC
68. Shim SY, Wang J, Asada N, et al. Protein 600 is a microtubule/endoplasmic reticulum-associated protein in CNS neurons. *J Neurosci* 2008;28:3604-14. DOI PubMed PMC
69. Tavana JP, Rosene M, Jensen NO, et al. RAB10: an Alzheimer's disease resilience locus and potential drug target. *Clin Interv Aging* 2019;14:73-9. DOI PubMed PMC
70. Ridge PG, Karch CM, Hsu S, et al; Alzheimer's Disease Neuroimaging Initiative. Correction to: Linkage, whole genome sequence, and biological data implicate variants in RAB10 in Alzheimer's disease resilience. *Genome Med* 2018;10:4. DOI PubMed PMC
71. Wang X, Li S, Wang H, Shui W, Hu J. Quantitative proteomics reveal proteins enriched in tubular endoplasmic reticulum of Saccharomyces cerevisiae. *Elife* 2017;6:e23816. DOI PubMed PMC
72. Geekiyanage H, Upadhye A, Chan C. Inhibition of serine palmitoyltransferase reduces Aβ and tau hyperphosphorylation in a murine model: a safe therapeutic strategy for Alzheimer's disease. *Neurobiol Aging* 2013;34:2037-51. DOI PubMed PMC
73. Liu L, Martin R, Chan C. Palmitate-activated astrocytes via serine palmitoyltransferase increase BACE1 in primary neurons by sphingomyelinases. *Neurobiol Aging* 2013;34:540-50. DOI PubMed PMC
74. Shahmoradian SH, Lewis AJ, Genoud C, et al. Lewy pathology in parkinson's disease consists of crowded organelles and lipid membranes. *Nat Neurosci* 2019;22:1099-109. DOI PubMed
75. Wang Q, Zheng J, Pettersson S, Reynolds R, Tan EK. The link between neuroinflammation and the neurovascular unit in synucleinopathies. *Sci Adv* 2023;9:eabq1141. DOI PubMed PMC
76. Rocha Cabrero F, Morrison EH. Lewy Bodies. In StatPearls; StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL); 2023.
77. Bendor JT, Logan TP, Edwards RH. The function of α-synuclein. *Neuron* 2013;79:1044-66. DOI PubMed PMC
78. Colla E. Linking the endoplasmic reticulum to parkinson's disease and Alpha-synucleinopathy. *Front Neurosci* 2019;13:560. DOI PubMed PMC
79. De Vos KJ, Mórotz GM, Stoica R, et al. VAPB interacts with the mitochondrial protein PTPIP51 to regulate calcium homeostasis. *Hum Mol Genet* 2012;21:1299-311. DOI PubMed PMC
80. Paillusson S, Gomez-Suaga P, Stoica R, et al. α-Synuclein binds to the ER-mitochondria tethering protein VAPB to disrupt Ca(2+) homeostasis and mitochondrial ATP production. *Acta Neuropathol* 2017;134:129-49. DOI PubMed PMC
81. Marongiu R, Spencer B, Crews L, et al. Mutant pink1 induces mitochondrial dysfunction in a neuronal cell model of Parkinson's disease by disturbing calcium flux. *J Neurochem* 2009;108:1561-74. DOI PubMed PMC
82. Joshi AS, Nebenfuehr B, Choudhary V, et al. Lipid droplet and peroxisome biogenesis occur at the same ER subdomains. *Nat Commun* 2018;9:2940. DOI PubMed PMC
83. Valadas JS, Esposito G, Vandekerkhove D, et al. ER lipid defects in neuropeptidergic neurons impair sleep patterns in parkinson's disease. *Neuron* 2018;98:1155-1169.e6. DOI PubMed
84. Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. *N Engl J Med* 2017;377:162-72. DOI PubMed
85. Kawamoto Y, Tada M, Asano T, et al. Phosphorylated CRMP1, axon guidance protein, is a component of spheroids and is involved in axonal pathology in amyotrophic lateral sclerosis. *Front Neurol* 2022;13:994676. DOI PubMed PMC
86. Vidal RL, Matus S, Bargsted L, Hetz C. Targeting autophagy in neurodegenerative diseases. *Trends Pharmacol Sci* 2014;35:583-91. DOI PubMed
87. Weydt P, Oeckl P, Huss A, et al. Neurofilament levels as biomarkers in asymptomatic and symptomatic familial amyotrophic lateral sclerosis. *Ann Neurol* 2016;79:152-8. DOI
88. Altman T, Ionescu A, Ibraheem A, et al. Axonal TDP-43 condensates drive neuromuscular junction disruption through inhibition of local synthesis of nuclear encoded mitochondrial proteins. *Nat Commun* 2021;12:6914. DOI PubMed PMC
89. Jokic N, Gonzalez de Aguilar JL, Dimou L, et al. The neurite outgrowth inhibitor Nogo-A promotes denervation in an amyotrophic lateral sclerosis model. *EMBO Rep* 2006;7:1162-7. DOI PubMed PMC

90. Teng FY, Tang BL. Nogo-A and Nogo-66 receptor in amyotrophic lateral sclerosis. *J Cell Mol Med* 2008;12:1199-204. DOI PubMed PMC
91. Kulczyńska-Przybik A, Mroczko P, Dulewicz M, Mroczko B. The implication of reticulons (RTNs) in neurodegenerative diseases: from molecular mechanisms to potential diagnostic and therapeutic approaches. *Int J Mol Sci* 2021;22:4630. DOI PubMed PMC
92. Chen MS, Huber AB, van der Haar ME, et al. Nogo-A is a myelin-associated neurite outgrowth inhibitor and an antigen for monoclonal antibody IN-1. *Nature* 2000;403:434-9. DOI
93. Bros-Facer V, Krull D, Taylor A, et al. Treatment with an antibody directed against Nogo-A delays disease progression in the SOD1G93A mouse model of Amyotrophic lateral sclerosis. *Hum Mol Genet* 2014;23:4187-200. DOI
94. Rodriguez CM, Bechek SC, Jones GL, et al. Targeting RTN4/NoGo-Receptor reduces levels of ALS protein ataxin-2. *Cell Rep* 2022;41:111505. DOI PubMed PMC
95. Dupuis L, Gonzalez de Aguilar JL, di Scala F, et al. Nogo provides a molecular marker for diagnosis of amyotrophic lateral sclerosis. *Neurobiol Dis* 2002;10:358-65. DOI
96. Pradat PF, Bruneteau G, Gonzalez de Aguilar JL, et al. Muscle Nogo-A expression is a prognostic marker in lower motor neuron syndromes. *Ann Neurol* 2007;62:15-20. DOI
97. Cadoni MPL, Biggio ML, Arru G, et al. VAPB ER-aggregates, a possible new biomarker in ALS pathology. *Cells* 2020;9:164. DOI PubMed PMC
98. Del Castillo U, Gnazzo MM, Sorensen Turpin CG, et al. Conserved role for Ataxin-2 in mediating endoplasmic reticulum dynamics. *Traffic* 2019;20:436-47. DOI PubMed PMC
99. Del Castillo U, Norkett R, Lu W, Serpinskaya A, Gelfand VI. Ataxin-2 is essential for cytoskeletal dynamics and neurodevelopment in drosophila. *iScience* 2022;25:103536. DOI PubMed PMC
100. Zhu PP, Hung HF, Batchenkova N, et al. Transverse endoplasmic reticulum expansion in hereditary spastic paraplegia corticospinal axons. *Hum Mol Genet* 2022;31:2779-95. DOI PubMed PMC
101. Mackay-Sim A. Hereditary spastic paraplegia: from genes, cells and networks to novel pathways for drug discovery. *Brain Sci* 2021;11:403. DOI PubMed PMC
102. Panza E, Meyyazhagan A, Orlacchio A. Hereditary spastic paraplegia: genetic heterogeneity and common pathways. *Exp Neurol* 2022;357:114203. DOI PubMed
103. Ramírez OA, Couve A. The endoplasmic reticulum and protein trafficking in dendrites and axons. *Trends Cell Biol* 2011;21:219-27. DOI PubMed
104. Blackstone C. Cellular pathways of hereditary spastic paraplegia. *Annu Rev Neurosci* 2012;35:25-47. DOI PubMed PMC
105. Kasher PR, De Vos KJ, Wharton SB, et al. Direct evidence for axonal transport defects in a novel mouse model of mutant spastin-induced hereditary spastic paraplegia (HSP) and human HSP patients. *J Neurochem* 2009;110:34-44. DOI
106. Tarrade A, Fassier C, Courageot S, et al. A mutation of spastin is responsible for swellings and impairment of transport in a region of axon characterized by changes in microtubule composition. *Hum Mol Genet* 2006;15:3544-58. DOI
107. Denton KR, Lei L, Grenier J, et al. Loss of spastin function results in disease-specific axonal defects in human pluripotent stem cell-based models of hereditary spastic paraplegia. *Stem Cells* 2014;32:414-23. DOI PubMed PMC
108. Rizo T, Gebhardt L, Riedlberger J, et al. Store-operated calcium entry is reduced in spastin-linked hereditary spastic paraplegia. *Brain* 2022;145:3131-46. DOI PubMed PMC
109. Qiang L, Piermarini E, Muralidharan H, et al. Hereditary spastic paraplegia: gain-of-function mechanisms revealed by new transgenic mouse. *Hum Mol Genet* 2019;28:1136-52. DOI PubMed PMC
110. Fassier C, Tarrade A, Peris L, et al. Microtubule-targeting drugs rescue axonal swellings in cortical neurons from spastin knockout mice. *Dis Model Mech* 2013;6:72-83. DOI PubMed PMC
111. Piermarini E, Akarsu S, Connors T, et al. Modeling gain-of-function and loss-of-function components of SPAST-based hereditary spastic paraplegia using transgenic mice. *Hum Mol Genet* 2022;31:1844-59. DOI PubMed PMC
112. Lim Y, Cho IT, Schoel LJ, Cho G, Golden JA. Hereditary spastic paraplegia-linked REEP1 modulates endoplasmic reticulum/mitochondria contacts. *Ann Neurol* 2015;78:679-96. DOI PubMed PMC
113. Wang B, Yu Y, Wei L, Zhang Y. Inhibition of ER stress improves progressive motor deficits in a REEP1-null mouse model of hereditary spastic paraplegia. *Biol Open* 2020:9. DOI PubMed PMC
114. Montenegro G, Rebelo AP, Connell J, et al. Mutations in the ER-shaping protein reticulon 2 cause the axon-degenerative disorder hereditary spastic paraplegia type 12. *J Clin Invest* 2012;122:538-44. DOI PubMed PMC
115. Akiduki S, Ikemoto MJ. Modulation of the neural glutamate transporter EAAC1 by the addicsin-interacting protein ARL6IP1. *J Biol Chem* 2008;283:31323-32. DOI PubMed
116. Fowler PC, O'Sullivan NC. ER-shaping proteins are required for ER and mitochondrial network organization in motor neurons. *Hum Mol Genet* 2016;25:2827-37. DOI PubMed
117. Novarino G, Fenstermaker AG, Zaki MS, et al. Exome sequencing links corticospinal motor neuron disease to common neurodegenerative disorders. *Science* 2014;343:506-11. DOI PubMed PMC
118. Apte MS, Joshi AS. Membrane shaping proteins, lipids, and cytoskeleton: recipe for nascent lipid droplet formation. *Bioessays* 2022;44:e2200038. DOI PubMed
119. Ramírez OA, Córdova A, Cerda M, et al. Ryanodine receptor-mediated Ca(2+) release and atlastin-2 GTPase activity contribute to IP(3)-induced dendritic Ca(2+) signals in primary hippocampal neurons. *Cell Calcium* 2021;96:102399. DOI PubMed

120. Fisher ER, Hayden MR. Multisource ascertainment of Huntington disease in Canada: prevalence and population at risk. *Mov Disord* 2014;29:105-14. DOI PubMed
121. novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. the huntington's disease collaborative research group. *Cell* 1993;72:971-83. DOI
122. Gauthier LR, Charrin BC, Borrell-Pagès M, et al. Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. *Cell* 2004;118:127-38. DOI
123. Gunawardena S, Her LS, Brusch RG, et al. Disruption of axonal transport by loss of huntingtin or expression of pathogenic polyQ proteins in Drosophila. *Neuron* 2003;40:25-40. DOI PubMed
124. Lee WC, Yoshihara M, Littleton JT. Cytoplasmic aggregates trap polyglutamine-containing proteins and block axonal transport in a Drosophila model of Huntington's disease. *Proc Natl Acad Sci USA* 2004;101:3224-9. DOI PubMed PMC
125. Mackay JP, Nassrallah WB, Raymond LA. Cause or compensation? *CNS Neurosci Ther* 2018;24:301-10. DOI PubMed PMC
126. Tang TS, Tu H, Chan EY, et al. Huntingtin and huntingtin-associated protein 1 influence neuronal calcium signaling mediated by inositol-(1,4,5) triphosphate receptor type 1. *Neuron* 2003;39:227-39. DOI PubMed PMC
127. Tang TS, Slow E, Lupu V, et al. Disturbed Ca^{2+} signaling and apoptosis of medium spiny neurons in Huntington's disease. *Proc Natl Acad Sci USA* 2005;102:2602-7. DOI PubMed PMC
128. Bezprozvanny I. Role of inositol 1,4,5-trisphosphate receptors in pathogenesis of Huntington's disease and spinocerebellar ataxias. *Neurochem Res* 2011;36:1186-97. DOI PubMed PMC
129. Holmes SE, O'Hearn E, Rosenblatt A, et al. A repeat expansion in the gene encoding junctophilin-3 is associated with Huntington disease-like 2. *Nat Genet* 2001;29:377-8. DOI PubMed
130. Moriguchi S, Nishi M, Komazaki S, et al. Functional uncoupling between Ca^{2+} release and afterhyperpolarization in mutant hippocampal neurons lacking junctophilins. *Proc Natl Acad Sci USA* 2006;103:10811-6. DOI PubMed PMC
131. Ueno S, Maruki Y, Nakamura M, et al. The gene encoding a newly discovered protein, chorein, is mutated in chorea-acanthocytosis. *Nat Genet* 2001;28:121-2. DOI
132. Kumar N, Leonzino M, Hancock-Cerutti W, et al. VPS13A and VPS13C are lipid transport proteins differentially localized at ER contact sites. *J Cell Biol* 2018;217:3625-39. DOI PubMed PMC
133. Yeshaw WM, van der Zwaag M, Pinto F, et al. Human VPS13A is associated with multiple organelles and influences mitochondrial morphology and lipid droplet motility. *Elife* 2019:8. DOI PubMed PMC
134. Chiurchiù V, Maccarrone M, Orlacchio A. The role of reticulons in neurodegenerative diseases. *Neuromolecular Med* 2014;16:3-15. DOI PubMed PMC
135. Wojnacki J, Nola S, Bun P, et al. Role of VAMP7-dependent secretion of reticulon 3 in neurite growth. *Cell Rep* 2021;35:109006. DOI
136. Zou Y, He W, Wang K, et al. Identification of rare RTN3 variants in Alzheimer's disease in Han Chinese. *Hum Genet* 2018;137:141-50. DOI PubMed
137. Alhajlah S, Thompson AM, Ahmed Z. Overexpression of reticulon 3 enhances CNS axon regeneration and functional recovery after traumatic injury. *Cells* 2021;10:2015. DOI PubMed PMC
138. Beetz C, Koch N, Khundadze M, et al. A spastic paraplegia mouse model reveals REEP1-dependent ER shaping. *J Clin Invest* 2013;123:4273-82. DOI PubMed PMC
139. Züchner S, Wang G, Tran-Viet KN, et al. Mutations in the novel mitochondrial protein REEP1 cause hereditary spastic paraplegia type 31. *Am J Hum Genet* 2006;79:365-9. DOI PubMed PMC
140. Hu J, Shibata Y, Zhu PP, et al. A class of dynamin-like GTPases involved in the generation of the tubular ER network. *Cell* 2009;138:549-61. DOI PubMed PMC
141. Liu X, Guo X, Niu L, et al. Atlastin-1 regulates morphology and function of endoplasmic reticulum in dendrites. *Nat Commun* 2019;10:568. DOI PubMed PMC
142. Rao K, Stone MC, Weiner AT, et al. Spastin, atlastin, and ER relocalization are involved in axon but not dendrite regeneration. *Mol Biol Cell* 2016;27:3245-56. DOI PubMed PMC
143. De Gregorio C, Delgado R, Ibacache A, Sierralta J, Couve A. Drosophila Atlastin in motor neurons is required for locomotion and presynaptic function. *J Cell Sci* 2017;130:3507-16. DOI PubMed
144. Krols M, Asselbergh B, De Rycke R, et al. Sensory neuropathy-causing mutations in ATL3 affect ER-mitochondria contact sites and impair axonal mitochondrial distribution. *Hum Mol Genet* 2019;28:615-27. DOI PubMed PMC
145. Chen S, Novick P, Ferro-Novick S. ER network formation requires a balance of the dynamin-like GTPase Sey1p and the Lunapark family member Lnp1p. *Nat Cell Biol* 2012;14:707-16. DOI PubMed PMC
146. Zhou X, He Y, Huang X, et al. Reciprocal regulation between lunapark and atlastin facilitates ER three-way junction formation. *Protein Cell* 2019;10:510-25. DOI PubMed PMC
147. Breuss MW, Nguyen A, Song Q, et al. Mutations in LNPK, encoding the endoplasmic reticulum junction stabilizer lunapark, cause a recessive neurodevelopmental syndrome. *Am J Hum Genet* 2018;103:296-304. DOI PubMed PMC
148. Liu Y, Xu XH, Chen Q, et al. Myosin Vb controls biogenesis of post-Golgi rab10 carriers during axon development. *Nat Commun* 2013;4:2005. DOI
149. Wang T, Liu Y, Xu XH, et al. Lgl1 activation of rab10 promotes axonal membrane trafficking underlying neuronal polarization. *Dev Cell* 2011;21:431-44. DOI

150. Homma Y, Fukuda M. Rabin8 regulates neurite outgrowth in both GEF activity-dependent and -independent manners. *Mol Biol Cell* 2016;27:2107-18. DOI PubMed PMC
151. Cheng CY, Wu JC, Tsai JW, et al. ENU mutagenesis identifies mice modeling Warburg Micro Syndrome with sensory axon degeneration caused by a deletion in Rab18. *Exp Neurol* 2015;267:143-51. DOI
152. Wu Q, Sun X, Yue W, et al. RAB18, a protein associated with Warburg Micro syndrome, controls neuronal migration in the developing cerebral cortex. *Mol Brain* 2016;9:19. DOI PubMed PMC
153. Genç Ö, Dickman DK, Ma W, et al. MCTP is an ER-resident calcium sensor that stabilizes synaptic transmission and homeostatic plasticity. *Elife* 2017;6:e22904. DOI PubMed PMC
154. Lindhout FW, Cao Y, Kevenaar JT, et al. VAP-SCRN1 interaction regulates dynamic endoplasmic reticulum remodeling and presynaptic function. *EMBO J* 2019;38:e101345. DOI PubMed PMC
155. Murphy SE, Levine TP. VAP, a versatile access point for the endoplasmic reticulum: review and analysis of FFAT-like motifs in the VAPome. *Biochim Biophys Acta* 2016;1861:952-61. DOI
156. Gómez-Suaga P, Pérez-Nievas BG, Glennon EB, et al. The VAPB-PTPIP51 endoplasmic reticulum-mitochondria tethering proteins are present in neuronal synapses and regulate synaptic activity. *Acta Neuropathol Commun* 2019;7:35. DOI PubMed PMC
157. Pavez M, Thompson AC, Arnott HJ, et al. STIM1 is required for remodeling of the endoplasmic reticulum and microtubule cytoskeleton in steering growth cones. *J Neurosci* 2019;39:5095-114. DOI PubMed PMC
158. Shim S, Zheng JQ, Ming GL. A critical role for STIM1 in filopodial calcium entry and axon guidance. *Mol Brain* 2013;6:51. DOI PubMed PMC
159. Dhanya SK, Hasan G. Purkinje neurons with loss of STIM1 exhibit age-dependent changes in gene expression and synaptic components. *J Neurosci* 2021;41:3777-98. DOI PubMed PMC
160. Zamponi E, Meehl JB, Voeltz GK. The ER ladder is a unique morphological feature of developing mammalian axons. *Dev Cell* 2022;57:1369-1382.e6. DOI PubMed
161. Li J, Yan B, Si H, et al. Atlastin regulates store-operated calcium entry for nerve growth factor-induced neurite outgrowth. *Sci Rep* 2017;7:43490. DOI PubMed PMC
162. Zhu Y, Zhang G, Lin S, et al. Sec61β facilitates the maintenance of endoplasmic reticulum homeostasis by associating microtubules. *Protein Cell* 2018;9:616-28. DOI PubMed PMC
163. Trotta N, Orso G, Rossetto MG, Daga A, Broadie K. The hereditary spastic paraplegia gene, spastin, regulates microtubule stability to modulate synaptic structure and function. *Curr Biol* 2004;14:1135-47. DOI PubMed