“At last in” the physiological roles of the tubular ER network

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Abstract In eukaryotic cells, the endoplasmic reticulum (ER) forms a continuous network of tubules and sheets. ER membranes are inter-connected by a class of dynamin-like GTPases termed atlastins (ATLs). Deletion or mutation of ATLs results in long and unbranched ER tubules in cells. Mutations in ATL1 in humans have been linked to the neurodegenerative disease hereditary spastic paraplegia. The basis of ATL-mediated membrane fusion has been studied extensively, but specific functions of ATL remain unclear. In this review, we summarize ER-related cellular processes that directly or indirectly involve ATL, including membrane trafficking, lipid metabolism, autophagy, microtubule dynamics, pathogen infections, calcium signaling, and protein homeostasis. These findings provide important clues for deciphering the physiological roles of the tubular ER network.

Keywords Atlastin, Membrane trafficking, Lipid metabolism, Autophagy, Microtubule dynamics, Pathogen infections, Calcium signaling, Protein homeostasis

INTRODUCTION

The endoplasmic reticulum (ER) is a very dynamic membrane-bound structure, with tubules constantly growing, retracting, and sliding along one another. Several integral membrane proteins are involved in ER shaping and remodeling. Membrane curvature of ER tubules is generated and stabilized by two classes of membrane proteins, the reticulons and REEPs (Voeltz *et al.* 2006). Connecting tubules in a network requires membrane fusion, which is mediated by dynamin-like GTPase atlastin (ATL) family proteins (Hu *et al.* 2009; Orso *et al.* 2009).

ATL was first identified as the product of a mutant gene, *SPG3A*, which causes a neurological disorder

called hereditary spastic paraplegia (HSP) (Zhao *et al.* 2001). The common features of HSP are progressive limb weakness, spasticity, and degeneration of the longest motor axons. Mammalian ATLs differ in tissue expression, with ATL1 expressed mainly in the neurons (Zhu *et al.* 2003), whereas ATL2 and ATL3 are expressed in peripheral tissues (Rismanchi *et al.* 2008). *Danio rerio* (zebrafish) has three *ATL* genes, with *atl1* expression enriched in the brain (Fassier *et al.* 2010), and *Drosophila melanogaster* and *Caenorhabditis elegans* have only one *ATL* gene (Rismanchi *et al.* 2008), which is ubiquitously expressed. In contrast, yeast contains a functional ortholog of ATL called synthetic enhancer of Yop1 (Sey1p), and plants have a Sey1p-related protein called root hair defective 3 (RHD3).

The fusion activity of ATLs was first deduced through genetic analysis in the model systems. Depletion of ATLs results in aberrant ER morphology, unbranched ER in mammalian cells (Hu *et al.* 2009), and fragmented ER in

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atl-null mutant flies (Orso *et al.* 2009). In yeast, the effects of Sey1p deletion on ER morphology are highlighted only upon simultaneous loss of the ER-tubule-forming proteins Rtn1p or Yop1p (Anwar *et al.* 2012; Hu *et al.* 2009), which results in less tubular ER. ER SNARE Ufe1p was proposed to complement the function of Sey1p in yeast (Anwar *et al.* 2012). Mutations or deletions of RHD3 in plants produce thick cable-shaped ER tubules (Zheng *et al.* 2004).

Direct evidence of ATL-mediated fusion was obtained using *in vitro* reconstitution with purified proteins. Purified *Drosophila* ATL, Sey1p, and RHD3 can catalyze artificial liposome fusion *in vitro* in a GTP-dependent manner (Anwar *et al.* 2012; Orso *et al.* 2009; Zhang *et al.* 2013). Strikingly, purified *Drosophila* ATL alone is sufficient to create and maintain a stable, branched, and tubular network (Powers *et al.* 2017). Of note, this network resembles the tubular ER in many aspects (Fig. 1). Although the scales are somewhat different, the *in vitro* network allows mechanistic studies of membrane structures maintaining ER-like morphology.

ATL family proteins contain an N-terminal GTPase domain, a three-helix-bundle (3HB) region, a trans-membrane (TM) region, and a C-terminal tail. Until recently, the membrane-bound region was thought to comprise two closely spaced TM segments, but it may actually consist of two intramembrane hairpin loops (Betancourt-Solis *et al.* 2018) similar to those in the reticulons and REEPs. Structural and biochemical studies have provided significant insight into the mechanism by which membranes are fused (Bian *et al.* 2011; Byrnes *et al.* 2013; Byrnes and Sondermann 2011; Liu *et al.* 2012, 2015; Yan *et al.* 2015). Upon GTP

binding, ATL forms dimers on either the same (*cis*) or opposing membranes (*trans*) through the GTPase domain. GTP cycles promote more *trans*-dimerization, which brings adjacent membranes close for fusion. In addition, the membrane curvature and lipid instability caused by hydrophobic segments in the amphipathic C-terminal helix also contribute to membrane fusion (Faust *et al.* 2015; Liu *et al.* 2012). Ergosterol, a cholesterol equivalent in yeast cells, was recently suggested to interact with Sey1p to promote ER membrane fusion in *Saccharomyces cerevisiae* (Lee *et al.* 2019).

As only the *trans*-dimers of ATL can eventually result in membrane tethering and fusion, the formation of *cis*-dimers appears to be a futile cycle (Liu *et al.* 2015). Furthermore, not all *trans*-dimers can cause successful fusion, as many of them convert to monomers without mediating fusion (Liu *et al.* 2015). When the GTPase activity is inhibited, the *in vitro* reconstituted network disassembles rapidly (Wang *et al.* 2013). Both the tethered and fused ER tubules give rise to junction-like structures in cells. Taken together, it appears that most of the three-way junctions generated by membrane fusion may actually consist of tethered, rather than fused, tubules (Wang *et al.* 2013). Such surprising findings have important physiological relevance as discussed below.

In this review, we examine multiple ATL-related functions and their potential roles in physiology and disease. Some pathways are impacted by the fusogenic activity of ATL and depend on the integrity of the ER morphology; others specifically rely on the presence of ATL (see Fig. 2 for a summary).

Fig. 1 Comparison of network in cell and *in vitro*. **A** COS-7 cells were transfected with HA-ATL1 and stained with anti-calreticulin (green) and anti-HA (red) antibodies. Bars: 5 μ m. **B** dmATL-reconstituted proteoliposomes were incubated with GTP. Bars: 5 μ m

Fig. 2 ATL-related cellular functions. ATL-related cellular functions are divided into fusion-dependent and fusion independent ones. The degree of correlation for each function is shown with connecting lines of different thickness

ATL IN COPII VESICLE PACKAGING

The vast majority of proteins that are transported to different cellular compartments or outside the cell require coat protein complex II (COPII) to exit the ER. COPII vesicles are formed at specialized sites within the ER, termed ER exit sites (ERESs). In *S. cerevisiae*, high-curvature domains of the ER are important for the organization of ERESs (Okamoto *et al.* 2012), indicating a role of tubular ER in regulating ERES formation.

The organization of the Golgi depends on efficient bidirectional vesicular transport with the ER. Inhibition of protein export from the ER disrupts Golgi organization, resulting in the formation of tubulovesicular Golgi clusters. Several studies have demonstrated that Golgi morphology and distribution are affected in some mammalian cell lines and plant cells lacking ATL family GTPases or upon expression of dominant-negative mutant forms (Chen *et al.* 2011; Namekawa *et al.* 2007; Rismanchi *et al.* 2008; Stefano *et al.* 2012; Zhao *et al.* 2016).

It was suggested recently that ATL plays a general role in regulating the timely exit of newly synthesized cargo into the secretory pathway. ATL loss-of-function results in decreased COPII formation and reduced ER export (Behrendt *et al.* 2019; Niu *et al.* 2019; Pawar *et al.* 2017). Deletion of ATL significantly slows the mobility of ER contents, which lead to a deficiency in cargo packaging. Intriguingly, ATL1 mutant R77A, which is capable of tethering but not fusing ER tubules, restores both protein flow and COPII formation. Conversely, transient fragmentation of the ER results in reduced efficiency of COPII packaging (Niu *et al.* 2019). The lateral tension of the membrane has been reported to greatly influence membrane fluidity (Quemeneur

et al. 2014). Thus, ATL-mediated membrane tethering may facilitate the mobility of cargo proteins by maintaining the lateral tension of the ER membrane. Similarly, the efficiency of inner nuclear membrane protein targeting, which appears to occur mostly via lateral diffusion in the connected ER and nuclear envelope membranes, is also affected in ATL-depleted cells due to impaired mobility of ER contents (Pawar *et al.* 2017).

Even though ATL deletion causes apparent defects in COPII formation, it does not engage the COPII component directly and, thus, has a general impact on a variety of cargos (Niu *et al.* 2019). It is not clear at this stage whether different ATLs regulate a subset of cargos. ATL possesses very little luminal exposure, making it limited for cargo sampling.

ATL IN ENDOCYTIC TRAFFICKING

The ER forms extensive membrane contact sites (MCSs) with endosomes in vertebrates. These MCSs are involved in multiple key processes regulating the shape and functions of endosomes, including biogenesis, fission, trafficking, cholesterol and calcium exchange (Raiborg *et al.* 2015). Several studies have suggested a central role of endosomes in regulating growth cone motility during axon growth and regeneration (Cosker *et al.* 2008; Sann *et al.* 2009; Steketee *et al.* 2011). During axon regeneration, ATL is required to concentrate the ER near the axon growth cone (Zhu *et al.* 2006). In zebrafish spinal neurons, ATL partially colocalizes with markers of early and late endosomes, which are scattered along axons and enriched in growth cones (Fassier *et al.* 2010).

Endocytic trafficking also plays important roles in regulating the activity and distribution of developmental signaling pathways (Villasenor *et al.* 2016). Functional synaptic vesicles are required for effective communication between neurons and their targets (Regehr *et al.* 2009; Zweifel *et al.* 2005). Retrograde endocytosis-regulated bone morphogenetic protein (BMP) signaling from postsynaptic muscles to presynaptic motor neurons is crucial for synaptic development and plasticity at larval neuromuscular junctions (NMJs) in *Drosophila* (Aberle *et al.* 2002; Marques *et al.* 2002; McCabe *et al.* 2003, 2004). Disruption of ATL1 in zebrafish motor neurons results in severe locomotion defects and impairs presynaptic function, possibly by upregulating BMP signaling (Fassier *et al.* 2010). Similarly, in *Drosophila*, downregulation or overexpression of ATL in motor neurons results in locomotor defects in larvae and adults (De Gregorio *et al.* 2017; Lee *et al.* 2008; Summerville *et al.* 2016), and correlates with

defects in axonal secretory organelle and presynaptic protein distribution (De Gregorio *et al.* 2017). Synaptic vesicle release is also impaired after ATL downregulation (De Gregorio *et al.* 2017; Lee *et al.* 2009). In cultured cortical rat neuron cells and HEK293T cells, expression of some SPG3A mutants exhibits a dominant-negative effect on trafficking of BMP receptor II (BMPRII) (Zhao and Hedera 2013). Taken together, these findings suggest that ATL regulates trafficking of signaling molecules, particularly in motor neurons.

In plant cells, endocytosis is critical for the intracellular trafficking and polarity of the transporters of the hormone auxin, a master regulator of plant growth (Jaillais and Chory 2010; Ljung 2013). In the absence of RHD3, the positioning and streaming of endosomes are affected, and the auxin transport machinery is disrupted, which subsequently increases the levels of auxin and inhibits root growth (Stefano *et al.* 2015). Collectively, ATL-mediated ER remodeling ensures a proper platform for endosomal contact, indirectly regulating endosomal function.

ATL IN LD BIOGENESIS

In eukaryotic cells, one of the key functions of the tubular ER is synthesizing, metabolising, and distributing lipids and sterols. Electron microscopy studies have revealed that lipid droplets (LDs) are closely associated with the ER membrane (Binns *et al.* 2010; Choudhary *et al.* 2015). LD formation tends to occur in ER tubules, where the high membrane curvature stress may help lens structure formation by locally disturbing the lipid bilayer (Jacquier *et al.* 2011; Thiam and Foret 2016). Perturbations of tubular ER structure, including changing the balance between sheets and tubules, or inhibiting the formation of tubular junctions, result in abnormal LD formation. ER-shaping proteins, including ATL (Klemm *et al.* 2013), REEP1 (Renvoise *et al.* 2016) and reticulons (Joshi *et al.* 2018; Wang *et al.* 2018), are reported to be involved in the biogenesis of LDs. Depletion of ATL in *C. elegans* or *Drosophila* results in small LDs and decreased tissue triglycerides (Klemm *et al.* 2013). In contrast, co-expression of REEP1 with ATL1 in mammalian cells induces the formation of very large LDs (Klemm *et al.* 2013). ATL triple KO in NIH-3T3 cells results in defects in adipocyte-like differentiation (Zhao *et al.* 2016). A microRNA, miR-30b-5p, regulates LD size and secretion in the mammary epithelial cells of transgenic mice by targeting *ATL2* (Le Guillou *et al.* 2019). Although many SPG mutants cause changes in LD morphology, whether LD abnormalities are related to the pathogenesis of HSP is unclear. Thus far, direct

interaction between ATL and known LD biogenesis machinery has not been reported. ATL likely acts independently by merging nascent LDs or contributes by regulating lipid mobility in the ER.

ATL IN ER-PHAGY

ER function and morphology are tightly linked to autophagy (Lamb *et al.* 2013). In response to starvation, autophagy is primarily thought to be a process that non-selectively degrades cellular material to meet cellular energy requirements. However, autophagy can also selectively target organelles and cellular structures that are damaged or need to be turned over (Stolz *et al.* 2014). The ER is primarily considered the major source of autophagosome membranes (Hayashi-Nishino *et al.* 2009; Yla-Anttila *et al.* 2009). Recent studies have demonstrated that, under starvation conditions, fragments of the ER are incorporated into autophagosomes and sent for lysosomal degradation in a process called ER-phagy (Dikic 2017; Mochida *et al.* 2015). Autophagy receptors are characterized by the ability to directly bind LC3/GABARAP family members through an LC3 interaction region (LIR; or GABARAP interaction motifs [GIMs]) and autophagic cargo (Rogov *et al.* 2014, 2017). Several ER surface proteins, including FAM134B (Khaminets *et al.* 2015), Rtn3 (Grumati *et al.* 2017), Sec62 (Fumagalli *et al.* 2016), CCPG1 (Smith *et al.* 2018), ATL3 (Chen *et al.* 2019), and TEX264 (Chino *et al.* 2019), have been shown to contain conserved domains that act as receptors that mediate ER turnover.

ATL3, the weakest fusogen of the ATL family, has been shown to function as an ER-phagy receptor to promote degradation of the tubular ER (Chen *et al.* 2019). ATL3 interacts specifically with the GABARAP subfamily via two GIM domains. The ATL3 mutations (Y192C and P338R), which are associated with hereditary sensory and autonomic neuropathy (HSAN), disrupt the interaction between ATL3 and GABARAP. The first GIM domain in ATL3 is also conserved in ATL1, and the Y192C mutation (Y196C in ATL1, an HSP-related mutation) localizes in this GIM, suggesting that dysfunction in ER-phagy may be involved in neurodegenerative disease pathogenesis. However, both GIMs are embedded in α -helical structures, making its accessibility questionable. Whether ATL3 influences ER-phagy or autophagy in general by acting as a receptor remains to be investigated.

Given that the ER is a continuous membrane system, it is critical to remodel the ER to segregate components targeted for autophagy from the rest of the ER. ATL2 has been shown to be such a remodeling factor (Liang *et al.*

2018). ATL2 colocalizes with FAM134B under both fed and starved conditions. When ATL2 is depleted, FAM134B overexpression fails to induce ER-phagy, indicating that ATL2 acts downstream of FAM134B in regulating ER-phagy (Liang *et al.* 2018). As FAM134B is mainly localized to the edge of ER sheets, ATL2 likely indirectly regulates sheet turnover. Intriguingly, three ATL family members have been suggested to functionally compensate for one another in regulating ER remodeling during ER-phagy.

ATL IN MICROTUBULE DYNAMICS

The ER is closely associated with microtubules in mammalian cells (Friedman and Voeltz 2011; Staehelin 1997; Terasaki *et al.* 1986; Voeltz *et al.* 2002). Several ER-resident membrane proteins, including STIM1 (Grigoriev *et al.* 2008), Climp63 (Klopfenstein *et al.* 1998), P180 (Ogawa-Goto *et al.* 2007), REEP1 (Park *et al.* 2010), and Sec61 β (Zhu *et al.* 2018), have been reported to interact directly with microtubules. Although this association is generally thought to regulate the morphogenesis and positioning of the ER, the alignment of ER tubules with the cytoskeleton is not always perfect. In addition, an ER network can be generated *in vitro* in the absence of an intact cytoskeleton (Dreier and Rapoport 2000). Thus, the specific function of the ER-microtubule interaction remains unclear. One hint is that microtubules may locally immobilize ER to promote efficient protein synthesis (Zhu *et al.* 2018). Another study reported that the localization of the ER in the axon is controlled by the crosstalk between ER-shaping proteins and microtubules. Local ER-microtubule interactions promote inter-stabilization of ER tubules and microtubule, and drive neuronal polarity (Farias *et al.* 2019).

In zebrafish, depletion of *atl* leads to severe defects in larval spinal motor neuron axons, namely, multiple aberrant branching associated with a lack of stable microtubules (Fassier *et al.* 2010). In a human neuronal model of SPG3A, axons show impaired growth (Zhu *et al.* 2014). In a *Drosophila* SPG3A model, the kinetics of microtubule assembly and disassembly are altered in muscles, which results in the abnormal accumulation of stable microtubules (Lee *et al.* 2009). The disruption of microtubules further results in defects in NMJs, which are responsible for muscle-neuron signaling. Importantly, the synapse and muscle defects in the *Drosophila* SPG3A model, and the axon growth defects in human SPG3A neurons, can be rescued by microtubule-binding agents (Lee *et al.* 2009; Zhu *et al.* 2014), emphasizing

the importance of the ATL-regulated tubular ER and microtubule interaction.

The ER-microtubule association is not only necessary for axon development, but also plays a role in dendrites. *Atln-1* is required for neuronal ER morphology in sensory neuron PVD in *C. elegans* (Liu *et al.* 2019). Interestingly, microtubule network is more stable in *atln-1* mutant worms. Both ER and microtubule extension into the branches are defective in the mutant animals. These results suggest ATL regulates dendritic branches and ATL-regulated ER morphology in turn influence microtubule network.

In *Arabidopsis*, RHD3 loss-of-function suppresses root waving, skewing, and epidermal cell file rotation (Yuen *et al.* 2005). Root movement is thought to be controlled by microtubules (Roy and Bassham 2014). The mutant does not respond to low doses of the microtubule-depolymerizing drug propyzamide, indicating that RHD3, like ATL in worm, may promote microtubule dynamics in *Arabidopsis* (Yuen *et al.* 2005). Consistently, taxol treatment, which stabilizes microtubule and decreases its dynamics, causes the formation of wavy root hairs as seen in the RHD3 mutant (Bibikova *et al.* 1999).

ATL IN INFECTION

The pathogenic bacterium *Legionella pneumophila* replicates in host cells within a distinct compartment termed the *Legionella*-containing vacuole (LCV) (Bruggemann *et al.* 2006; Hubber and Roy 2010; Isberg *et al.* 2009). LCVs communicate with the endosomal, retrograde, and secretory vesicle trafficking pathway, and eventually associate with the ER (Robinson and Roy 2006; Swanson and Isberg 1995). Interestingly, a proteomic analysis of purified LCVs identified *Dictyostelium discoideum* Sey1 (*DdSey1*, ATL3 homolog) and Rtn4a as conserved LCV host components (Hoffmann *et al.* 2014). *DdSey1* was further found to promote intracellular replication of *L. pneumophila* in host cells (Steiner *et al.* 2017). Live cell imaging revealed that *DdSey1* regulates LCV expansion at later stages of infection (Steiner *et al.* 2017). Thus, *DdSey1* is involved in mediating extensive ER remodeling around LCVs during their maturation.

ATL is also targeted by viral infection. Many plant RNA viruses achieve successful infection by remodeling host cellular membranes (Cotton *et al.* 2009). Turnip mosaic virus (TuMV), a positive-strand RNA virus, remodels the ER to generate viral vesicles. These viral vesicles are sites of viral replication, intracellular movement, and intercellular spread (Cotton *et al.* 2009; Grangeon *et al.* 2012, 2013). Viral replication in primary

infected cells and the intercellular movement of TuMV were recently reported to be impaired in RHD3 mutant plants with delayed maturation of the viral vesicles (Movahed *et al.* 2019). Hijacking of the endomembrane system, including the ER, is a common effort by other viruses. ATLs have been shown to facilitate Zika virus replication (Monel *et al.* 2019). In addition, ATL3 specifically appears at the replication site, co-localizing with viral proteins NS2A and NS2B3. ATL-deleted cells have been used to test for infections by flavivirus (Neufeldt *et al.* 2019). A lack of ATL2 causes replication organelle defects, whereas a lack of ATL3 affects virion assembly. Specific interactions between ATLs and viral replication-related complexes were assessed. Thus, individual ATLs were proposed to play differentiated and specific roles during viral infections. The role of ATL1 in HIV-1 replication has also been investigated (Shen *et al.* 2017).

ATL IN CALCIUM SIGNALING

The connection between the ER and plasma membrane (PM) plays important roles in regulating store-operated calcium entry (SOCE) (Lam and Galione 2013). STIM1 is a Ca^{2+} sensor located at the ER membrane. When Ca^{2+} levels are low in the ER, STIM1 oligomerizes and migrates to the ER-PM junctions to interact with the Orai channel in the PM and activate SOCE (Hogan *et al.* 2010).

Disruption of the tubular ER network can cause defects in SOCE. It has been shown that knockdown of Rtn4a, which results in a less tubular ER, can inhibit SOCE in cultured mouse embryonic fibroblasts (Jozsef *et al.* 2014). Recently, it was revealed that ATL may also be involved in this pathway. ATL1 overexpression or depletion, or the expression of dominant-negative mutants inhibits SOCE (Li *et al.* 2017). Ca^{2+} has been suggested to play key roles in regulating the outgrowth of dendrites and axons (Mattson *et al.* 1988, 1990). ATL1 and overexpression of its GTP-binding mutation K80A in neuroendocrine PC-12 cells reduce nerve growth factor (NGF)-induced neurite outgrowth in PC12 cells in a SOCE-dependent manner (Li *et al.* 2017). These findings suggest another potential mechanism underlying ATL-related neuronal disorders.

ATL IN PROTEIN HOMEOSTASIS

Effective ER quality control of newly synthesized proteins is important for maintaining protein homeostasis. When the ability of the ER to balance protein synthesis

demand and capacity is compromised, cells experience stress. In conditions of ER stress, a largely conserved signaling pathway, the unfolded protein response (UPR), is activated (Ron and Walter 2007). The UPR measures unfolded protein levels in the ER and adjusts the production of ER chaperones and degradation factors to maintain acceptably low levels of misfolded proteins in the lumen.

In *Arabidopsis*, loss of RHD3 negatively affects UPR activation by interfering with the function of the master regulator inositol-requiring enzyme 1 (IRE1) (Lai *et al.* 2014). RHD3 acts upstream of IRE1 and is required for proper clustering and activation (Lai *et al.* 2014). In *C. elegans*, perturbation of the IRE1 arm of the UPR pathway causes loss of PVD dendritic branches (Wei *et al.* 2015). Although dendrite morphogenesis seems normal in *atln-1* single mutant, *ire-1* and *atln-1* double mutants demonstrate enhanced PVD dendrite arborization defects (Liu *et al.* 2019). These findings suggest that ATL1 functions synergistically with IRE1 in regulating the UPR. In mammalian cells, the basal level of Bip, an ER stress marker, is elevated in the ATL1/2/3 triple KO NIH-3T3 cells at steady state. There is increased sensitivity in the KO cells at lower concentrations of inducers of ER stress (Zhao *et al.* 2016). It was also shown recently that another ER stress marker, phosphorylated eIF2 α , is increased in COS-7 and HeLa cells lacking ATL2 and ATL3, possibly by affecting proteins exiting the ER (Niu *et al.* 2019).

ER stress is well known to be relevant to neurodegenerative disorders (Martinez *et al.* 2017; Remondelli and Renna 2017). However, a recent study suggested that impaired protein synthesis also results in dendritic spinogenesis defects (Shih and Hsueh 2016), as inhibition of protein synthesis using the translation blocker cycloheximide and mTOR inhibitor rapamycin reduced dendritic spine density in cultured hippocampal neurons. Valosin-containing protein (VCP) is an AAA+ ATPase that functions as a chaperone regulating diverse cellular processes determined by its cofactors (Meyer *et al.* 2012; Yamanaka *et al.* 2012). VCP, together with its cofactor P47 and ATL1, regulates dendritic spine formation in neurons by influencing the efficiency of protein synthesis (Shih and Hsueh 2016). These results suggest a potential role of ATL1 in the regulation of protein synthesis and dendritic spinogenesis, likely indirectly.

PERSPECTIVE

Several neurodegenerative disorders are caused by genetic defects in proteins involved in the shaping and

dynamics of the ER, suggesting that ER dysfunction may contribute to the loss of neuronal function. However, the precise mechanism of ER involvement is unclear. The studies summarized in this review offer insight into cellular functions in which ATL may be involved. Currently, ER formation, synapse development, lipid metabolism, microtubule stability, membrane trafficking, calcium homeostasis, autophagic pathways, and BMP signaling seem to be attractive targets. In-depth investigation will gradually become available using ATL loss-of-function mouse models and reconstituted ER networks. Further understanding of ATL will provide critical insights into the underlying pathophysiology and allow development of potential therapeutic strategies for HSP.

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Compliance with Ethical Standards

Conflict of interest Li Lü, Liling Niu, and Junjie Hu declare that they have no conflict of interest.

Research Involving Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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