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Review

Advances in molecular and cell biology of dystonia: Focus on torsinA

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ABSTRACT

During the last two decades, our knowledge on the genetic bases of Mendelian forms of dystonia has expanded significantly. This has translated into the generation of multiple cell and animal models to explore the neurobiological bases of this hyperkinetic movement disorder. A majority of these studies have focused on DYT1 dystonia, caused by dominant mutations in the gene encoding for the protein torsinA. Since its discovery, work in multiple laboratories helped identify the subcellular localization of torsinA, key structural features, functionally important physical interactions and biological pathways and physiological events influenced by torsinA. Moreover, recent experimental work indicates potential shared pathogenic pathways between different genetic forms of dystonia. This review will summarize our current knowledge on the molecular and basic biological features of torsinA and its dysfunction when carrying disease-causing mutation, identifying future research priorities and proposing a model of dystonia pathogenesis that might extend beyond DYT1.

1. Introduction

During the second half of the XX century, the concept of dystonia evolved from consideration as a psychiatric illness to its classification as a neurological disorder on the way towards an era of biological studies (Newby et al., 2017). A key resulting milestone was the discovery of the gene responsible for DYT1 (*TOR1A*), the most common childhood-onset primary generalized dystonia, over 20 years ago (Ozelius et al., 1997; Ozelius et al., 2011). Since then, an increasing number of genes linked to Mendelian forms of dystonia have been discovered (**reviewed by Jinnah in this issue**). This expanding knowledge is advancing our understanding of the biological bases of this hyperkinetic movement disorder.

The chronology of gene discovery gave DYT1 a head start, being the form of dystonia more intensively investigated in the laboratory. It is hoped that understanding the neurobiology of DYT1 will shed light on shared pathogenesis with other etiological forms. A biological classification of dystonia could drive rational therapeutic design. This review will focus on molecular and cell biological features of DYT1, highlighting recent findings to propose a mechanistic neurobiological model of pathogenesis.

2. Genetics of *TOR1A*-related disease

The efforts aimed at identifying the genetic bases of dominant, early-onset generalized torsion dystonia (EOTD) culminated in the identification of a sequence variant in a gene initially named *DYT1*, subsequently *TOR1A* (Ozelius et al., 1997). Almost all patients with *TOR1A*-related dystonia harbor the same mutation, an in-frame GAG deletion (ΔGAG) in the last of its 5 exons. This recurrent variant results in the loss of a pair of glutamic acid residues (p.302/p.303delE) in a protein named torsinA (torsinA(ΔE)). Most cell and animal models harbor this variant.

Private variants in *TOR1A* have been reported in a few patients with dystonia with experimental evidence supporting pathogenicity. Although very rare, they provide valuable information on torsinA function. Some lead to an early onset of a severe phenotype (p.R288Q) (Zirn et al., 2008), while others cause milder, adult-onset phenotypes (p.F205I; p.A14_P15del; p.E121K) (Bhagat et al., 2016; Hettich et al., 2014; Vulinovic et al., 2014; Calakos et al., 2010). *TOR1A* variants were also identified in single subjects with dystonia and myoclonic features, who were later found to harbor known mutations in the DYT11 gene (myoclonus dystonia) (Doheny et al., 2002; Leung et al., 2001; Ritz et al., 2009). Finally, *TOR1A* haplotypes have been linked to adult-onset idiopathic dystonia in some populations, an association not found in others (Groen et al., 2013).

A recent development has been the identification of biallelic mutations in *TOR1A* in six subjects from five different families, all presenting with congenital arthrogryposis and severe neurological features. Mutations, found in homozygosity or compound heterozygosity,

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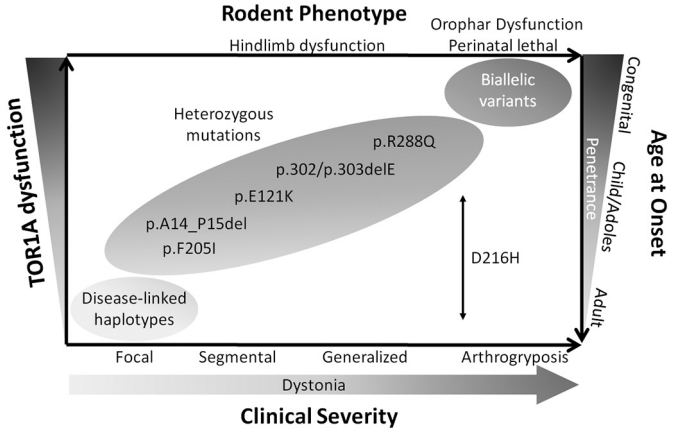

Fig. 1. *TOR1A* variants linked to human disease. A trinucleotide deletion in *TOR1A* causing the deletion of a glutamic acid residue in torsinA (p.302/p.303DdelE) was identified as the cause of DYT1 dystonia. Since then, additional sequence variants in *TOR1A* have been linked to human disease and several animal models of DYT1 have been generated. This information allows us to hypothesize that differences on how these variants quantitatively impair torsinA function would determine clinical penetrance, age at onset and severity. This ranges from haplotypes reported as a risk factor for sporadic adult onset focal dystonia in population studies to private heterozygous variants causing dystonia with varying severity, or biallelic mutations that cause a severe congenital phenotype. A single nucleotide polymorphism underlying an aminoacid change (D216H) would slightly influence torsinA function, mot only affecting penetrance of dominant mutations, but also representing a risk factor for adult onset focal dystonia in the general population.

include p.302/p.303delE, p.G318S, p.R288* and p.T321Rfs*6 (Kariminejad et al., 2017; Reichert et al., 2017; Isik et al., 2018; Cascalho and Goodchild, 2018). It would be interesting to determine if the phenotype of arthrogryposis in these patients does not result from primary neuromuscular dysfunction, but in fact represents severe congenital dystonia. These reports suggest that there is a spectrum of *TOR1A*-disease resulting from different sequence variants in *TOR1A*, likely resulting in a continuum of residual torsinA function, as illustrated in Fig. 1. This would determine penetrance, age at onset and severity of phenotype, somewhat mirrored in animal models. Heterozygous *Tor1a*(ΔGAG) *knockin* mice exhibit subtle hindlimb dysfunction, whereas homozygous mutations cause a severe congenital syndrome with oropharyngeal dysfunction and perinatal death(Goodchild et al., 2005; Dang et al., 2005).

A key genetic feature in DYT1 is reduced penetrance. Only about a third of carriers of the GAG deletion develop dystonia within a developmental window. The role of genetic and environmental factors on penetrance has been partly addressed(Martino et al., 2013). A single nucleotide polymorphism in *TOR1A*, encoding for an aminoacid change in torsinA (D216H), influences penetrance. The 216H allele protects against the development of dystonia in GAG deletion carriers, a more robust effect when present in the wild type allele (Risch et al., 2007). Interestingly, this allele might also influence the susceptibility to sporadic dystonia (Kamm et al., 2008). The identification of factors that influence penetrance is a research priority. If modifiable, they could help devise strategies to prevent the development dystonia in mutation carriers.

Following the cloning of *TOR1A*, three additional gene members of the mammalian torsin family were identified, *TOR1B*, *TOR2A* and *TOR3A* (Ozelius et al., 1999). While a detailed discussion of this family is beyond the scope of this review, *TOR1B* deserves mention. Despite ubiquitous expression of *TOR1A* across all tissues, the DYT1 phenotype is restricted to the nervous system. Animal studies indicate that this is a consequence of functional overlap provided by *TOR1B*, a closely related homologue expressed in all tissues except in neurons (Jungwirth et al., 2010; Kim et al., 2010; Tanabe et al., 2016). Expressing its resulting protein, torsinB, in neurons rescues phenotypes caused by *TOR1A* dysfunction. Therefore, manipulating neuronal *TOR1B* expression with small molecules or gene-transfer approaches is a potential therapeutic strategy.

3. Molecular biology of *TorsinA*

3.1. Structure

Upon cloning the *TOR1A* gene, primary sequence analysis of torsinA revealed a 332 amino acid protein belonging to the AAA protein superfamily (ATPases Associated with diverse cellular Activities) (Ozelius et al., 1997). A signal peptide sequence is followed by a hydrophobic stretch upstream Walker A and B motifs, predicted to bind and hydrolyze ATP, respectively (Breakefield et al., 2001). Three-dimensional structural models were generated *in silico* through alignment with phylogenetically related AAA proteins, such as ClpA and ClpB, for which the crystal structure has been solved (Kock et al., 2006; Zhu et al., 2008). Successful production of recombinant torsinA helped validate some structural predictions (Zhu et al., 2008; Kustedjo et al., 2003). These analyses indicate that the mutated glutamic acid is located in a carboxy-terminal α-helix, highlighting key functional roles for nearby conserved cysteine residues. Addressing its quaternary structure, biochemical studies show that torsinA assembles into homo- or hetero-hexamers (Goodchild et al., 2015). However, attempts to resolve the three-dimensional structure of torsinA were repeatedly unsuccessful until the group of Thomas Schwartz obtained functionally relevant structural information for torsinA in complex with activating cofactors (Demircioglu et al., 2016), as discussed later.

3.2. Subcellular localization and processing

TorsinA is imported into the endoplasmic reticulum (ER) where the signal sequence is cleaved (Liu et al., 2003) and the downstream hydrophobic stretch anchors it to the ER membrane (Vander Heyden et al., 2011). Two asparagine residues (N143 and N158) remain fully modified by high mannose glycans that are not processed into complex sugars (Hewett et al., 2000; Kustedjo et al., 2000; Gonzalez-Alegre and Paulson, 2004), indicating that torsinA does not exit the early secretory pathway. The N-terminal hydrophobic domain is key for ER retention, driving torsinA preferentially to ER sheets (Vander Heyden et al., 2011). Similar to torsinA(WT), the disease-linked ΔE form is imported into the ER lumen but redistributes to the perinuclear space of the nuclear envelope (NE), contiguous with the ER lumen (Gonzalez-Alegre and Paulson, 2004; Goodchild and Dauer, 2004; Naismith et al., 2004). The structure of the eukaryotic NE is conserved, with inner and outer nuclear membranes (INM and ONM, respectively) separated by a narrow perinuclear space. TorsinA(ΔE) overexpression causes ultrastructural defects in the NE, and the generation of NE-derived blebs or cytoplasmic inclusions (Goodchild et al., 2005; Gonzalez-Alegre and Paulson, 2004; Goodchild and Dauer, 2004; Naismith et al., 2004; Grundmann et al., 2012). This is modulated by the D216H polymorphism(Kock et al., 2006), indirectly linking this cytological phenotype to disease penetrance. Quantitative analysis of these inclusions has been used for high-throughput screening studies (Rittiner et al., 2016).

Important posttranslational processing of torsinA occurs in the ER lumen. Under ER stress, its hydrophobic domain is cleaved through a proteolytic event likely regulated by the redox state of two adjacent cysteines, mobilizing it from the ER membrane (Zhao et al., 2016). Two other cysteines near the carboxy-terminal region (Cys280 and Cys319) are also functionally important. Cys319 is essential in nematodes, and both residues regulate ATP/ADP and substrate binding (Zhu et al., 2008; Zhu et al., 2010). As a result, the redox state of conserved cysteines in the highly oxidizing ER environment likely regulates torsinA function. Overexpression of protein disulfide isomerases (PDIs), ER

proteins that catalyze disulfide bond formation, reduces levels of torsinA, indicating that the state of these cysteines is key for stability (Zacchi et al., 2017). Moreover, torsinA carrying dystonia-causing variants forms abnormal disulfide bond-dependent dimers in overexpression systems (Hettich et al., 2014; Vulinovic et al., 2014; Gonzalez-Alegre and Paulson, 2004; Gordon and Gonzalez-Alegre, 2008). Future studies should determine if abnormal crosslinking occurs in DYT1 human brain tissue or induced pluripotent stem cell (iPSC)-derived neurons.

TorsinA is a stable glycoprotein, preferentially degraded through the non-selective process of macroautophagy. On the other hand, torsinA(ΔE) is more efficiently targeted to the ubiquitin proteasome system (UPS) for degradation by FBG1 and other ubiquitin ligases, with lower steady-state levels than the wild type protein (Gordon and Gonzalez-Alegre, 2008; Giles et al., 2008). This could have important implications. As discussed later, torsinA(ΔE) possibly exerts dominant negative effect over the wild type (WT) protein. Thus, the torsinA(ΔE): (WT) expression ratio would be important in DYT1 pathogenesis. Interventions that selectively accelerate the degradation of torsinA(ΔE) by the UPS could be therapeutically helpful. The interplay between the redox state, oligomerization, stability and function of torsinA needs a more in depth mechanistic scrutiny.

3.3. TorsinA-protein interactions

TorsinA(WT) and (ΔE) reside preferentially in the ER and perinuclear space of the NE, exiting the secretory pathway for degradation by the UPS. Consequently, functionally important torsinA interactions must take place in the ER/NE lumen, where binding partners have been identified.

3.3.1. LAP1/LLUL1

An innovative cell-based torsinA-protein interaction assay led to the initial identification of LAP1 (lamina-associate polypeptide 1) and LULL1 (luminal domain like LAP1) (Goodchild and Dauer, 2005), subsequently confirmed by others (Naismith et al., 2009). These monotypic transmembrane proteins bind torsinA though their carboxy-terminal lumenal domain, while their nucleoplasmic or cytosolic amino-terminus are responsible for their NE (LAP1) and ER (LULL1) localization (Goodchild and Dauer, 2005; Naismith et al., 2009). Initially thought to have ATPase activity, torsinA lacks a key consensus aminoacid required for ATP hydrolysis. LAP1 and LULL1 act as cofactors, “donating” this function through a physical interaction with torsinA, which requires LULL1 or LAP1 binding to hydrolyze ATP. Through LULL1 or LAP1 binding, torsinA oligomers hydrolyze ATP and disassemble (Brown et al., 2014; Chase et al., 2017; Laudermilch and Schlieker, 2016; Rose et al., 2015; Zhao et al., 2013). In the ER, LULL1 triggers the redistribution of torsinA from the ER to the NE, whereas downregulation of LULL1 rescues the ER localization of torsinA(ΔE) (Vander Heyden et al., 2009). The DYT1 mutation destabilizes this interaction, resulting in defective torsinA activation (Demircioglu et al., 2016; Zhu et al., 2010; Naismith et al., 2009; Vander Heyden et al., 2009). Collectively, this data demonstrates that LULL1 and LAP1 catalyze the otherwise weak ATPase activity of torsinA through a physical interaction, regulating its oligomerization and subcellular localization. The DYT1-causing mutation interferes with the activation of torsinA, an event possibly influenced by the redox-regulated sensor II motif of torsinA (Zhu et al., 2008). Interestingly, published data supports that the redox-state of torsinA could be the switch that triggers conformational changes required for binding and activation by LAP1 or LULL1 (Zhu et al., 2010). A reasonable hypothesis is that the convergence of cytoplasmic and nucleoplasmic signals delivered through LULL1 and LAP1 with redox-driven conformational changes signaled within the ER lumen are the upstream factors that govern the dynamic behavior of torsinA, regulating its subcellular localization and access to different sets of binding partners. This, in turn, would affect different downstream aspects of cellular biology.

3.3.2. Protein quality control machinery

In the ER, the main lumenal chaperone, BiP, binds and stabilizes torsinA (Zacchi et al., 2014), which also binds calnexin (ER transmembrane chaperone) (Naismith et al., 2009) and several proteins implicated in ER-associated degradation (ERAD): Derlin-1, VCP/p97, VIMP and FBG1 (Nery et al., 2011; Gordon et al., 2012). These interactions might simply reflect the effects of the ER protein quality control machinery on torsinA as ER cargo. However, based on its chaperone activity and results of biological studies discussed below, torsinA is likely both a client and effector of the ER protein quality control machinery.

3.3.3. LINC complexes

The perinuclear space of the NE, where torsinA(ΔE) is preferentially located and torsinA(WT) is also found, is delimited by the INM (facing the nucleoplasm) and ONM (facing the cytosol). Relevant torsinA-interactors occur in this space. The INM protein SUN1 is required for the NE accumulation of torsinA(ΔE) and influences the presence of torsinA(WT) in this subcompartment, indicating direct binding or an indirect interaction (Vander Heyden et al., 2009; Jungwirth et al., 2011). TorsinA also binds the luminal KASH domain of nesprins (Nery et al., 2008), a group of ONM proteins linked to the cytoskeleton and SUN proteins to form LINC complexes (Linker of Nucleoskeleton and Cytoskeleton) (Saunders and Luxton, 2016).

3.3.4. Other TorsinA binding partners

A novel protein called Printor (protein interactor of torsin), in contrast to LAP1 and LULL1, binds torsinA only in the ATP-free form, not when bound to ATP or in the presence of the ΔE mutation. There is little follow up on the mechanistic bases and significance of this interaction (Giles et al., 2009; Valastyan and Lindquist, 2011). TorsinA also interacts with the subunit 4 of CSN signalosome (CSN4), influencing levels of the synaptic regulator snapin and stonin2 (Granata et al., 2011). Where this physical interaction takes place is unclear. Not surprisingly, torsinA also interacts with torsinB and torsin3A (Naismith et al., 2009). Other reported torsinA binding partners that require confirmation, as they reside outside the ER or NE lumen, include tyrosine hydroxylase (O'Farrell et al., 2009) and kinesin light chain 1 (Kamm et al., 2004).

4. Cellular neurobiology

A reasonable first step to identify biological events that lie downstream torsinA function is to evaluate how its expression influences physiology in its immediate living environment, the ER and NE. Subsequently, expanding the focus beyond organelle biology to other cellular mechanisms influenced by torsinA function could move us a step forward to fill the gap between the gene defect and systems neuroscience aspects of DYT1. Although much remains to be understood, significant progress has been made in this front.

4.1. Endoplasmic reticulum and nuclear envelope biology

4.1.1. Glycoprotein homeostasis and eIF2α signaling

As an ER-NE resident protein phylogenetically related to AAA chaperones, different research groups have addressed a potential role for torsinA in processing and trafficking of ER cargo and the response to proteotoxic ER stress. TorsinA regulates the trafficking of polytopic ER client proteins (Torres et al., 2004) and a secreted luciferase reporter protein in cultured cells, including DYT1 patient-derived fibroblasts (Hewett et al., 2007). How exactly torsinA influences this process remains unknown, but several studies point towards quality control mechanisms. TorsinA exhibits chaperone activity *in vitro* (Burdette et al., 2010) and could help fold substrates into their native conformation. In

addition, reactive cysteines in torsinA might act as donors or acceptors in the oxidative folding process or in the assembly of disulfide-linked multiprotein complexes. As a result, torsinA function would influence trafficking through the early secretory pathway. Moreover, torsinA has been implicated in ERAD, a process in which terminally misfolded proteins or non-assembled components of oligomers are retro-translocated to the cytosol for degradation by the proteasome (Nery et al., 2011). Studies in nematodes support a role for torsinA in the maintenance of ER protein homeostasis (Chen et al., 2010), perhaps by regulating the fate of ER cargo towards forward trafficking or degradation.

When a threshold of misfolded proteins in the ER lumen is reached, a well-orchestrated adaptive program known as the unfolded protein response (UPR) is launched to restore homeostasis (Hetz and Saxena, 2017). Three mechanistically distinct parallel branches of the UPR exist. In one of them, the ER membrane protein PERK (protein kinase RNA-like endoplasmic reticulum kinase) oligomerizes and phosphorylates eIF2α (Eukaryotic Initiation Factor 2 alpha), essential for translational initiation and a master regulator of the response to various external stressors (Moon et al., 2018). Through eIF2α phosphorylation, cells reduce the global anabolic burden. Although initial cell-based studies yielded conflicting evidence on the role of torsinA on ER stress responses (Baptista et al., 2003; Cho et al., 2014; Gordon et al., 2011; Thompson et al., 2014; Hewett et al., 2003), recent independent studies identified dysregulation of eIF2α signaling in DYT1 models with supportive human data (Rittiner et al., 2016; Beauvais et al., 2016; 2018, 2019). Dysfunction of eIF2α-regulated physiological events and rescue by pharmacological manipulation of eIF2α phosphorylation indicate the potential significance of these findings. However, we still do not know if these changes are pathogenic or compensatory, whether they are related to the appearance of dystonia or simply represent subclinical neurobiological signatures of torsinA(ΔE) expression.

4.1.2. Lipid metabolism

The laboratory of Rose Goodchild recently addressed a neglected aspect of torsinA biology: its effects on lipid biogenesis and metabolism (Grillet et al., 2016). LULL1-driven redistribution of torsinA to the NE causes an expansion of the nuclear membrane and a quantitatively significant increase in total lipid content. Interestingly, torsinA influences the functional balance between lipin, a key enzyme in the synthesis of energy-storing lipids such as triacylglycerol, and CCT (CTP:phosphocholine cytidylyltransferase) involved in membrane biosynthesis. Overexpression of lipin rescues biochemical, cellular and survival phenotypes in Torsin-null flies. Therefore, through its actions on these enzymes, torsinA could act as a switch to direct lipid metabolism towards energy storage or membrane biogenesis (Cascalho et al., 2017; Teleman, 2016) and influence synaptic physiology (Lauwers et al., 2016). The underlying mechanism remains to be elucidated, but energy metabolism is intimately linked to redox regulation. Moreover, lipin is a downstream target of mTOR signaling, also found to be dysregulated in DYT1 models. The role of torsinA on lipid metabolism should be confirmed in mammalian neurons, and perhaps with brain magnetic resonance spectroscopy or with lipidomic analysis of CSF or peripheral tissues in DYT1 mutation carriers. These novel findings have significant translational potential, as lipid metabolism is amenable to pharmacological intervention.

4.1.3. Calcium homeostasis

Calcium is a ubiquitous second messenger critical for neuronal function and survival that regulates multiple signaling pathways. Calcium homeostasis is preserved by regulated entry of extracellular calcium through the plasma membrane or release from intraneuronal stores, such as the ER (Bollimuntha et al., 2017). A proteomic analysis of DYT1 *knockin* mouse brain tissue detected dysregulation of several calcium-regulated proteins (Beauvais et al., 2016). Moreover, abnormal calcium currents, levels and calcium-dependent channel function have been measured in striatal neurons in response to the pharmacological manipulation of dopaminergic, cholinergic, glutamatergic and opioid receptors (Dang et al., 2012; Iwabuchi et al., 2013a; Iwabuchi et al., 2013b; Pisani et al., 2006; Ponterio et al., 2018; Sciamanna et al., 2014; Sciamanna et al., 2011). Nevertheless, these findings are unlikely a result of direct torsinA actions on calcium physiology, but rather reflect upstream neurotransmission defects. However, by altering stonin2 levels, torsinA(ΔE) causes the accumulation of a calcium sensor, synaptotagmin1, on the cell surface potentially affecting transport (Granata et al., 2011). This could underlie the reported influence of torsinA on synaptic vesicle physiology (Granata et al., 2009; Granata and Warner, 2010; Kakazu et al., 2012; Warner et al., 2010; Granata et al., 2008). Finally, DYT1 *knockin* cerebellar slices exhibit abnormal calcium physiology, more pronounced in the presence of acute ER stress (Beauvais et al., 2016). We need to reach a better mechanistic understanding of the link between torsinA function and calcium physiology before exploring pharmacological correction of calcium defects as a potential therapeutic strategy.

4.1.4. Nucleo-cytoplasmic transport

The initial reports of the abnormal accumulation of torsinA(ΔE) in the NE shifted biological studies to this subcellular compartment. By disrupting the NE, torsinA(ΔE) could alter nucleo-cytoplasmic transport. A relatively insensitive reporter assay of nuclear import transport through nuclear pore complexes (NPC) showed no effect of torsinA(ΔE) expression in cultured cells (Gonzalez-Alegre and Paulson, 2004). More recently, however, different groups identified NPC defects in DYT1 models. Genetic deletion of the torsinA homologue OOC-5 in *Caenorhabditis elegans* results in mislocalization of nucleoporins with impaired nuclear import kinetics (VanGompel et al., 2015), with similar findings in torsinA-null mouse (Pappas et al., 2018a). Collectively, these reports suggest that torsinA influences NPC biogenesis during neuronal maturation and loss of torsinA function renders them unable to evolve through their normal developmental process.

A recently described non-canonical, NPC-independent form of transport across the NE involves large ribonucleoprotein particles (RNP) that exit the nucleus for local protein synthesis and are essential for synapse formation (Speese et al., 2012). These RNP particles are assembled in the nucleus and exported by budding through the INM and ONM, in a mechanism similar to nuclear egress by herpes simplex virus (HSV). Remarkably, torsinA plays a major role in RNP envelopment and, in the absence of torsin, RNPs are sequestered in the perinuclear space and never reach their synaptic target preventing local protein synthesis and synaptic bouton development (Jokhi et al., 2013). Consistent with this finding, torsinA and LULL1 also affect HSV egress (Gyorgy et al., 2018; Maric et al., 2011; Turner et al., 2015) suggesting that LULL1 redirects torsinA to the NE to facilitate trans-NE export. This novel mechanism provides another very intriguing link between torsinA function, translational regulation and synaptic function, emerging topics in dystonia research.

4.1.5. Nucleo-cytoskeletal coupling

LINC complexes are very dynamic structures defined by the presence of transmembrane ONM (KASH domain-containing) and INM (SUN domain-containing) proteins that interact in the perinuclear space functionally linking nucleoskeleton to cytoskeleton (Saunders and Luxton, 2016). This interaction is key for centrosome positioning or cell migration, among other events, critical in neurogenesis and maintenance of neuronal polarization. By directly or indirectly binding their lumenal domains, torsinA influences the localization of SUN and KASH-domain proteins in the perinuclear space, regulating their interactions (Vander Heyden et al., 2009; Jungwirth et al., 2011; Nery et al., 2008; VanGompel et al., 2015; Pappas et al., 2018a). Moreover, SUN1 is required for the NE localization of torsinA(ΔE) (Jungwirth et al., 2011). Functional studies indicate that, though actions on LINC complexes, torsinA steers cellular events that depend on nucleo-cytoplasmic

coupling. TorsinA-null mice fibroblasts exhibit delayed nuclear polarization and cell migration in a wound-healing assay (Nery et al., 2008), perhaps due to defective nuclear movement during centrosome orientation (Saunders et al., 2017). *Caenorhabditis elegans* lacking the torsinA homologue ooc-5 exhibit defects in cell polarity and asymmetric division (Basham and Rose, 1999; Basham and Rose, 2001). Therefore, by altering the normal dynamics of LINC complexes in neurons, torsinA(ΔE) could interfere with the developmental generation and functional maintenance of the brain network implicated in dystonia.

4.2. Synaptic function and neurodevelopment

Various aspects of neuronal biology have been experimentally implicated in dystonia pathogenesis. This review will focus on two emerging areas of research, neuroplasticity-neurodevelopment and the nigrostriatal system. It should be emphasized that this does not indicate that they are primarily responsible for dystonia, but rather that each provide us with a helpful experimental framework to evaluate how torsinA function affects neuronal biology that then can be expanded to other cellular or physiological systems to determine their potential relevance, significance and therapeutic potential.

Because DYT1 appears to be a neurodevelopmental disorder, the potential influence of torsinA(ΔE) on synaptic plasticity and neurodevelopment has been addressed (Dang et al., 2005; Tanabe et al., 2016; Maltese et al., 2018; Dauer, 2014; Liang et al., 2014). TorsinA(ΔE) has been linked to synaptic dysfunction at different levels, including deficient transport of RNP to synapses, impaired synaptic vesicle recycling and defective synaptic plasticity as discussed earlier. In addition, there is evidence of impairment of neurite formation (Hewett et al., 2006), which could be linked to the reported plasticity defects. Along with its involvement in the integrated stress repose, the exquisite regulatory capabilities of eIF2α signaling have been harnessed to regulate key neuronal events under homeostatic conditions, such as synaptic plasticity and neurite extension (Moon et al., 2018; Di Prisco et al., 2014; Costa-Mattioli et al., 2007). Abnormal synaptic plasticity in DYT1 *knockin* mice is rescued by pharmacological manipulation of eIF2α signaling (Rittiner et al., 2016). It is possible that defective protein processing by torsinA(ΔE) causes abnormal basal eIF2α signaling, indirectly influencing synaptic plasticity.

TorsinA is essential for postnatal survival in mice (Goodchild et al., 2005; Dang et al., 2005) and biallelic mutations cause a severe neurological phenotype in humans (Cascalho and Goodchild, 2018; Kariminejad et al., 2017; Reichert et al., 2017; Isik et al., 2018). How loss of torsinA function causes these early neurodevelopmental phenotypes requires additional investigation. Nevertheless, what this data tells us is that there is a critical interaction between torsinA function in neurons and neurodevelopment. An ontogenic neurobiological analysis that temporally profiles the sequence of events that follow torsinA(ΔE) expression during neuronal differentiation could help us discriminate initial pathogenic events from compensatory or non-specific downstream changes of torsinA dysfunction. Combining studies in neurons generated from DYT1-patient derived iPSCs with developing brain of DYT1 *knockin* mice is a reasonable experimental approach to address this question.

4.3. Dopaminergic and cholinergic systems

The nigrostriatal dopaminergic system is at the core of many movement disorders (Gittis and Kreitzer, 2012). The neuroanatomical bases of dystonia go beyond this system and involve the cerebellum and other areas of the sensorimotor network. However, nigrostriatal disorders frequently exhibit dystonia and pharmacological manipulation of this system can both cause and alleviate this hyperkinetic syndrome (Goodchild et al., 2013; Eskow Jaunarajs et al., 2015; Wichmann, 2008). Therefore, understanding the influence of torsinA on this system is relevant, potentially shedding light on the pathogenesis of DYT1 and other forms of dystonia. While an exhaustive review is beyond the goal of this article, there is evidence of striatal and dopaminergic dysfunction in patients with DYT1 dystonia by functional imaging, their response to anticholinergic agents and deep brain stimulation of the globus pallidus and subthalamic nucleus (Balint et al., 2018; Karimi and Perlmutter, 2015; Fox and Alterman, 2015; Carbon et al., 2010).

Studies in animal models demonstrate cell-autonomous impairment in dopamine release by nigral neurons (Page et al., 2010; Song et al., 2012; Balcioglu et al., 2007). Moreover, there is extensive evidence of abnormal function in striatal projection neurons, including microstructural changes (Maltese et al., 2018; Song et al., 2013), although with significant complexity. Some reports attribute it to a downstream effect of cholinergic dysfunction (Eskow Jaunarajs et al., 2015; Pappas et al., 2015; Pappas et al., 2018b; Maltese et al., 2014; Sciamanna et al., 2012a; Sciamanna et al., 2012b), although other neurotransmitter and signaling systems have been implicated (Pisani et al., 2006; Ponterio et al., 2018; Sciamanna et al., 2014; Sciamanna et al., 2011; Sciamanna et al., 2012b; Martella et al., 2009; D'Angelo et al., 2017; Napolitano et al., 2010; Zimmerman et al., 2017). Experimental data also supports a cell-autonomous effect of torsinA function in medium spiny neurons. Many of the publications just referenced report impaired function of dopamine 2 receptors (D2R) in DYT1. Striatum-specific tor1a conditional knockout mice exhibit reduced striatal D2R, indicating a cell-autonomous effect (Yokoi et al., 2011). Moreover, this is likely a consequence, at least in part, of defective D2R processing in the ER that leads to accelerated degradation (Bonsi et al., 2019). The mechanism underlying all these striatal findings, how they interact with each other and whether they are linked to the appearance of dystonia remains to be determined. However, these reports demonstrate the presence of relevant basal ganglia dysfunction in DYT1, including cell autonomous consequences of torsinA dysfunction in dopaminergic and dopaminoceptive neurons. Not being a simple dopamine deficiency state as other forms of dystonia (Lee et al., 2018), efforts should focus on understanding the physiological consequences of torsinA dysfunction on striatal projection neurons, where the nigral dopaminergic system, cholinergic interneurons and influence of cortical glutamatergic terminals converge to modulate movement. Understanding how torsinA influences striatal function could undeniably help us better understand its role in other components of the defective brain network.

5. Mechanism of disease pathogenesis

Understanding the molecular mechanism of disease pathogenesis is key for therapeutic design. Genetic studies in various animal models indicate that a loss of torsinA function causes DYT1(Goodchild et al., 2005; Dang et al., 2005; Liang et al., 2014). This could result from haploinsufficiency or *via* a dominant negative effect of torsinA(ΔE) over torsinA(WT) (Breakefield et al., 2001). Although torsinA(ΔE) exhibits reduced torsinA activity, cell and animal-based studies mostly support the latter mechanism. TorsinA forms hexamers, disassembled upon LULL1-binding resulting in shuttling of torsinA to the NE. The insertion of one or more torsinA(ΔE) units in these oligomers likely makes them dysfunctional (Breakefield et al., 2001). Therefore, the DYT1 mutation is likely to cause a loss of torsinA function in *Cis* (loss of function in torsinA(ΔE)) and in *Trans* (rendering torsinA(WT) dysfunctional when co-existing in oligomers). Molecular and biological evidence supports this model. TorsinA(ΔE) recruits torsinA(WT) from the ER to the NE, and the ER localization of torsinA(WT) is rescued by RNAi-mediated, allele-specific downregulation of torsinA(ΔE) (Gonzalez-Alegre et al., 2005). Similarly, torsinA(ΔE) expression impairs trafficking of a reporter protein in DYT1 patient fibroblasts, a defect rescued by allele-specific silencing of torsinA(ΔE) (Hewett et al., 2007; Hewett et al., 2008). Tor1a null mice develop ultrastructural abnormalities in the neuronal NE (Goodchild et al., 2005), and transgenic rats overexpressing torsinA(ΔE) with two normal tor1a endogenous alleles develop similar NE structural abnormalities, whereas those

overexpressing torsinA(WT) do not (Grundmann et al., 2012). Finally, lowering endogenous levels of torsinA(WT) or overexpressing torsinA(ΔE) similarly reduce levels of snapin (Granata et al., 2011; Granata et al., 2008). Interestingly, aberrant disulfide-linked torsinA dimerization in the presence of disease-causing mutations (Hettich et al., 2014; Vulinovic et al., 2014; Gonzalez-Alegre and Paulson, 2004; Gordon and Gonzalez-Alegre, 2008) could represent the molecular basis for this dominant negative effect. A consequence of this model is that selectively downregulating torsinA(ΔE) could restore torsinA(WT) function, as shown in different publications (Beauvais et al., 2019; Gonzalez-Alegre et al., 2005; Hewett et al., 2008; Gonzalez-Alegre et al., 2003). On the other hand, a model of haploinsufficiency would require torsinA(WT) replacement, which could be challenging as overexpressing torsinA(WT) is potentially deleterious (Maric et al., 2011; Grundmann et al., 2007).

6. Molecular convergence with other forms of dystonia

As we expand our knowledge on the neurobiology of torsinA, it is critical to ascertain which of the many biological consequences of torsinA(ΔE) expression are linked to the clinical expression of dystonia. A major drawback is the animal models that genetically replicate the human disease do not exhibit dystonia. A matter of debate in the dystonia field for years, rodents are clearly a helpful system to study torsinA biology, but less valuable to mirror the genotype-phenotype correlation observed in humans (Meringolo et al., 2018; Jinnah et al., 2008). How could we determine which of the biological pathways dysfunctional in DYT1 models are related to dystonia? An indirect approach is to identify molecular or biological changes that are also found in other forms of dystonia. While not definitive, if dysfunction of the same pathway is present in various genetically unrelated forms of dystonia, it is more likely to be relevant. However, with the exception of very rare pathogenic variants in genes implicated in dopamine synthesis (Lee et al., 2018), we still lack a unifying hypothesis of how sequence variants in apparently unrelated genes converge on similar clinical phenotypes.

Two main areas of convergence between DYT1 and other inherited forms of dystonia have recently emerged. EIF2α dysfunction is also found in DYT6 (Zakirova et al., 2018), another form of primary dystonia caused by dominant mutations in the transcription factor THAP1. THAP1 function has been linked to the cellular response to ER stress (Nayak et al., 2014). Moreover, and DYT6 models exhibit similar synaptic plasticity defects to those reported in DYT1, similarly rescued by pharmacological manipulation of eIF2α phosphorylation. The gene responsible for DYT16, PRKRA, is an activator of the eiF2α kinase PKR. DYT16 patient fibroblasts display enhanced and persistent phosphorylation of PKR and eiF2α under ER stress (Vaughn et al., 2015). Going beyond eiF2α, other translational control pathways could play a role in different forms of dystonia, such as mTOR, which could link energy sensing to protein and lipid metabolism. Although more work is needed, this new exciting area of dystonia research harbors significant translational potential.

In addition to DYT1 and the dopa-responsive dystonias, other genetic forms link dystonia to dopaminergic and cholinergic systems. Mutations in GNAL cause adult onset local or segmental dystonia (DYT25) (Fuchs et al., 2013). GNAL encodes for a G-protein enriched in medium spiny neurons that mediates the actions of dopamine and adenosine (Alcacer et al., 2012; Herve, 2011; Pelosi et al., 2017). DYT6 patients exhibit reductions in striatal D2R similar to those seen in DYT1 (Carbon et al., 2009). Moreover, defective postsynaptic dopaminergic signaling in striatal neurons has been implicated in other hyperkinetic movement disorders, such as levodopa-induced or tardive dyskinesias (**reviewed by Standaert and Calabresi in this issue**). Thus, similar defective signal integration in striatal projections neurons could be at the core of hyperkinetic movement disorders beyond inherited dystonia, perhaps sharing pharmacological targets in the striatum.

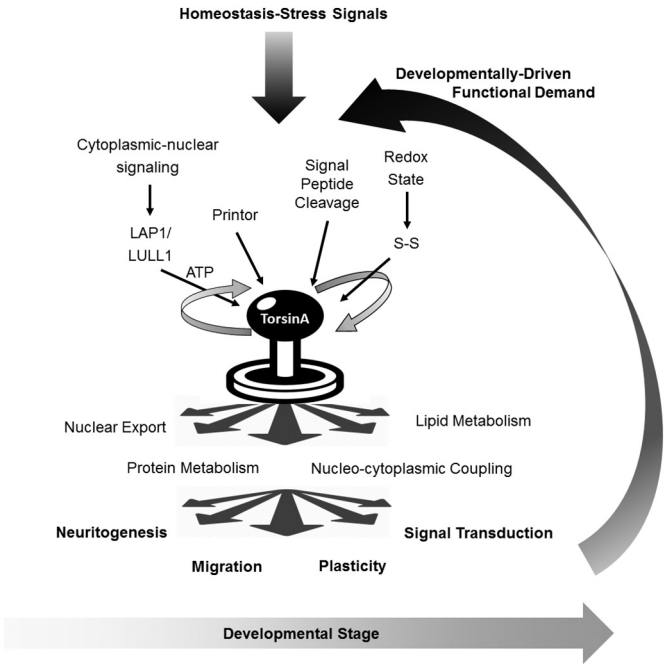

Fig. 2. A model of torsinA function. Molecular information reported by multiple investigators indicates that torsinA could function as a versatile switch that integrates multiple signals. In this model, developmentally-determined functional demand and homeostatic state signals converge on torsinA to modify its conformation *via* post-translational modifications (such as disulfide links or proteolytic cleavage) and cofactor biding (ATP-bound or ATP-free). This results in multiple potential conformations that dynamically modify its subcellular localization and interactome within the ER and NE, regulating its functional output. For instance, during a period of synaptogenesis, torsinA function could be directed towards facilitating protein and RNA transport to the synapse and promote lipid biogenesis in an energy-depend manner. In "quiescent" stages, its conformation would favor energy storage. A restricted conformational repertoire of torsinA(ΔE) would impair its ability to integrate these signals. As a result, torsinA(ΔE) would be trapped in a state that promotes lipid biogenesis, interferes with protein processing and impairs the neuronal ability to respond to redox signaling, among others.

7. A working hypothesis for torsinA function

The experimental evidence summarized in this review can be applied towards a hypothesis-generating exercise of how torsinA normally functions and how dystonia-linked variants would derange neuronal biology when mutated. Obviously, this simply represents a framework to be experimentally challenged in suitable model systems (Fig. 2).

After entering the ER and cleavage of the signal peptide, the amino-terminal hydrophobic domain anchors torsinA to the membrane while it undergoes glycosylation and proper folding in the lumen assisted by chaperones and oxidoreductases. Once mature, torsinA seems to act as a multidimensional switch influencing an array of intersecting pathways: from protein and lipid anabolic regulation to energy metabolism, nuclear export or nucleo-cytoskeletal coupling. What are the signals that flip this functional switch in torsinA? The redox state of cysteines, including intra-and inter-molecular disulfide bonds, could be targeted by upstream signals to rearrange torsinA interactions. Some conformations might favor binding of different substrates to assist their trafficking or facilitate downstream signals, while others could redirect hexamers to interact with LULL1 in an ATP-bound form before hydrolysis and transit to the NE. LAP1 and LULL1 themselves could also add another layer of regulation being effectors of nuclear and cytoplasmic signals relayed to torsinA. Finally, a stress-driven proteolytic event likely releases torsinA from regulation by membrane proteins, changing its repertoire of interacting partners. Therefore, a combination of redox-driven

conformational stages, stress-triggered proteolysis, ATP/ADP availability and signaling through LAP1/LULL1 (and perhaps other cofactors such as printor) would influence the status of the torsinA switch and, consequently, its downstream effects.

One could envision that during key neurodevelopmental periods, the switch would direct torsinA function towards facilitating trafficking of protein complexes to the plasma membrane, enhancing lipid biogenesis, favoring nuclear export of RNPs destined to neurites and facilitating nuclear positioning for proper polarization or migration. In adult mature neurons, the switch could be repositioned to maintain homeostasis depending on the cell subtype. For instance, in striatal projection neurons, it could help integrate multiple internal and external signals while maintaining their high metabolic demand, aiming to generate a precise output. Multiple configurations of this switch are likely possible in different subtypes of neurons, at different developmental stages, and under homeostatic or stress conditions. This tightly orchestrated process would be altered when homeostasis is challenged triggering stress responses. In this scenario, torsinA would refocus its functional properties to help restore homeostasis. Therefore, it is important to experimentally query torsinA function in the right cytological context, at different developmental stages and under homeostatic or stress conditions.

The presence of dystonia-causing mutations would interfere with the normal function of torsinA by altering its ability to respond to the signals that govern its behavior. The switch would be disabled with a limited repertoire of actions. Based on findings in cell-based and animal models, this defective conformation could be stuck in favor of unchecked membrane biogenesis while impairing nuclear export, protein trafficking and with restricted influence on dynamic nuclear positioning. This could evidently have multiple downstream consequences, from abnormal receptor composition in the neuronal surface affecting function, to defective migration and integration into a network, or defective synaptic physiology, among others. While it is unclear which of those abnormal events lead to dystonia, as some could be subclinical consequences of torsinA(ΔE) expression, it is likely that they act synergistically. Acting individually on one of them, with selective targeting of lipid metabolism, eIF2α signaling or nuclear export, among others, is less likely to provide therapeutic benefit. Therefore, efforts aimed at normalizing neuronal biology in DYT1 should be focused on restoring torsinA function in the right tissue and at the right time. Alternatively, therapies could bypass neuronal biology and aim to correct the resulting dysfunctional network, as currently done with deep brain stimulation or anticholinergics.

Due to the limitations mentioned earlier, preclinical trials in animal models of DYT1 are of limited help in terms of clinical efficacy, although could identify deleterious effects on an intervention (for instance, if we interfere with a compensatory mechanism). This should not delay progress in therapeutic development. Once minimally acceptable proof of concept has been reached and safety IND-enabling studies are completed for a given therapeutic intervention, it should be advanced towards clinical trials. If the field wants to identify novel ways to alter the natural history of *TOR1A*-related disease, scientists, physicians and patients must be willing to embrace the risk of testing therapies in patients with limited preclinical evidence of efficacy.

8. Conclusion

In summary, during the last decade we have significantly advanced our understanding of the neurobiological mechanisms underlying DYT1 dystonia. While many pieces of the puzzle still need to be put together, a clearer view of dystonia pathogenesis is emerging. At the molecular level, post-translational modifications and conformational changes in torsinA seem to govern a dynamic interactome resulting in actions on protein and lipid metabolism. At the biological level, these molecular events likely regulate critical neurodevelopmental and synaptic plasticity events that, if disrupted at the right ontogenic stage, interfere with the normal function of a sensorimotor network that results in the appearance of dystonia. Over the next few years, research priorities include the identification of upstream regulatory mechanism of torsinA function, defining how torsinA integrates signals to modulate protein, lipid and energy metabolism and linking these molecular events to abnormal physiology. Moreover, from a therapeutic point of view, a key unanswered question is whether correction of torsinA function reverses the appearance of dystonia after symptom onset. Taking advantage of recent advances in molecular interventions, this could catalyze the development of novel therapeutic approaches for DYT1. Finally, the identification of the factors that determine disease penetrance in DYT1 and other forms of dystonia should be approached through the organized effort of many investigators as this question could hide the key to preventive strategies in mutations carriers.

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