Chapter 10
Myotubularin Phosphoinositide Phosphatases in Human Diseases

Leonela Amoasii, Karim Hnia and Jocelyn Laporte

Abstract The level and turnover of phosphoinositides (PIs) are tightly controlled by a large set of PI-specific enzymes (PI kinases and phosphatases). Mammalian PI phosphatases are conserved through evolution and among this large family the dual-specificity phosphatase (PTP/DSP) are metal-independent enzymes displaying the amino acid signature Cys-X5-Arg-Thr/Ser (CX5RT/S) in their active site. Such catalytic site characterizes the myotubularin 3-phosphatases that dephosphorylate PtdIns3*P* and PtdIns(3,5)P_2 and produce PtdIns5*P*. Substrates of myotubularins have been implicated in endocytosis and membrane trafficking while PtdIns5*P* may have a role in signal transduction. As a paradox, 6 of the 14 members of the myotubularin family lack enzymatic activity and are considered as dead phosphatases. Several myotubularins have been genetically linked to human diseases: MTM1 is mutated in the congenital myopathy X-linked centronuclear or myotubular myopathy (XLCNM) and MTMR14 (JUMPY) has been linked to an autosomal form of such disease, while MTMR2 and MTMR13 are mutated in Charcot-Marie-Tooth

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(CMT) neuropathies. Furthermore, recent evidences from genetic association studies revealed that several other myotubularins could be associated to chronic disorders such as cancer and obesity, highlighting their importance for human health. Here, we discuss cellular and physiological roles of myotubularins and their implication in human diseases, and we present potential pathological mechanisms affecting specific tissues in myotubularin-associated diseases.

Abbreviations

AAV	Adeno-associated-virus
BIN1	Bridging integrator 1 gene coding fo amphiphysin 2
CC	Coiled-coil
CMT	Charcot-Marie-Tooth neuropathies
CMTX	X-linked inherited CMT
CNM	Centronuclear myopathy
Dlg1	Disks large 1
DI-CMT	Dominant inherited CMT
DRM	Desmin related myopathies
DRCM	Desmin related cardiomyopathies
PTP/DSP	Protein Tyrosine Phosphatase/Dual-specificity phosphatase
DNM2	Dynamin 2
EC	Excitation–contraction
EGF	Epidermal growth factor
$GEFS^{+}$	Generalized epilepsy with febrile seizures plus
ING2	Inhibitor of growth 2
KO	Knockout
MTM1	Myotubularin
MTMR	Myotubularin-related
NCV	Nerve conduction velocity
NF-L	Neurofilament light chain protein
Pi3K68D	PI 3-kinase class II
PIs	Phosphoinositides
PtdIns	Phosphatidylinositol
PHD	Plant homeodomain
PH-GRAM	Pleckstrin homology, glucosyltransferases, rab-like GTPase activators and myotubularins
RID	Rac-induced recruitment domain
RYR1	Ryanodine receptor
SAP97	Synapse associated 97
SID	Set-interacting domain
XLCNM	X-linked recessive form of centronuclear myopathy

Introduction

Phosphoinositide (PI) lipids are essential components of eukaryotic cell membranes. PIs, the phosphorylated derivatives of phosphatidylinositol (PtdIns), regulate fundamental biological processes including cell growth and survival, membrane trafficking, and cytoskeletal dynamics (Di Paolo and De Camilli 2006). PIs comprise less than 1 % of cell lipids, yet they play very important roles in major signal transduction pathways, serving as docking sites for signaling effectors and as precursors of secondary messengers. The inositol head group of PtdIns can be reversibly phosphorylated at three positions, 3, 4, and 5, and all seven PI isoforms, including three monophosphorylated (PtdIns3*P*, PtdIns4*P,* and PtdIns5*P*), three bisphosphorylated [PtdIns(3,4)P_2, PtdIns(3,5)P_2, and PtdIns(4,5)P_2], and one trisphosphorylated [PtdIns(3,4,5)P_3] species have been identified in eukaryotic cells (Fig. 10.1). The level and turnover of PIs are tightly controlled by a large set of PI-specific enzymes (PI-kinases and phosphatases). Found on the cytosolic side of membrane bilayers, PIs are readily accessible to PI-kinases and phosphatases capable of attaching and removing phosphate groups, respectively, and to phospholipases that cleave the lipids. PIs species are enriched in distinct intracellular membranes and thus each form of PIs may serve as a marker of membrane subdomains or organelles. However, the dynamics of PIs more than their absolute concentration at a given subdomain is probably underlying their specific functions. For example, the PtdIns3*P* is the most represented PI signature on early endosomes and a ligand for a large number of endosomal proteins (Gillooly et al. 2000; Simonsen et al. 1998). The bulk of PtdIns3*P* pool is generated directly on endosomes by the phosphorylation of PtdIns at the 3-position by PI 3-kinases (Murray et al. 2002). Subsequently, phosphorylation of PtdIns3*P* into PtdIns(3,5)P_2 by PIKfyve 5-kinase on endosomes is thought to generate docking sites for the recruitment of cytosolic factors that control outgoing traffic from early and late endosomes and multivesicular bodies formation (Odorizzi et al. 1998, 2000). The localization of PtdIns5*P*, a low abundance PI species that can be generated by either phosophorylation of PtdIns by PIKfyve or dephosphorylation of PtdIns(3,5)P_2 or PtdIns(4,5)P_2 by myotubularins or 4-phosphatases, respectively, remains under investigation (Coronas et al. 2007; Tronchere et al. 2004; Ungewickell et al. 2005). However, specific mass assays and imaging using high affinity probes like the plant homeodomain (PHD) of the inhibitor of growth 2 (ING2) lead several groups to suggest that PtdIns5*P* may act as a second messenger both in the cytoplasm and the nucleus (Gozani et al. 2003, 2005; Morris et al. 2000). The amount of PtdIns5*P* can be increased by different stimuli such as thrombin in platelets, insulin in 3T3-L1 cells, T cell receptor engagement, increased tyrosine kinase activity, and stress signals (Grainger et al. 2011; Morris et al. 2000; Pizarro-Cerda and Cossart 2004; Sbrissa et al. 2001, 2002). In addition, an increase in PtdIns5*P* was reported during the G1 phase of the cell cycle (Clarke et al. 2001). Infection by the intracellular pathogens *Shigella flexneri* or *Salmonella Typhimurium* also results in increased amounts of PtdIns5*P* in host cells supporting that pathogens divert the PIs metabolism to

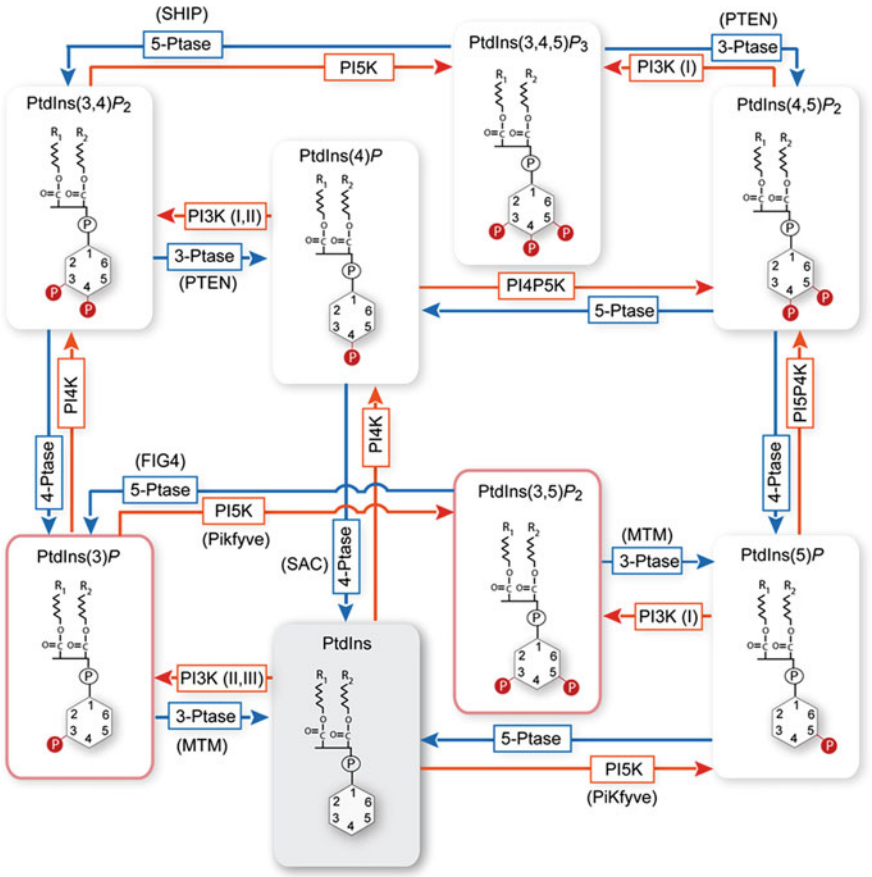

Fig. 10.1 Integration of myotubularins in the PI metabolism and PI-metabolizing reactions. The phosphatidylinositol (*PtdIns*) is an acidic (anionic) phospholipid that in essence consists of a phosphatidic acid backbone, linked via a phosphate group to inositol ring. PtdIns is subjected to reversible phosphorylation on three of the five free hydroxyl groups on the inositol ring (D3, D4 and D5), and this generates seven possible PI species. The PI metabolism is spatially and temporally regulated in the cell through controlled recruitment and activation of the different PI kinases (*red arrow*) and phosphatases (*blue arrow*). The majority of these metabolizing-enzymes are implicated in a variety of human diseases such as the 3-phosphatase (3-Ptase) PTEN, the 5-phosptahases SHIP and FIG4, and the 5-kinase (PI5 K) PIKfyve. Myotubularins are 3-phosphatase that dephosphorylate both PtdIns3,5-bisphosphate (PtdIns3,5P_2) and the PtdIns3*P* to PtdIns5*P* and PtdIns, respectively. Three catalytically active myotubularin-like proteins have been implicated in neuromuscular diseases; MTM1 and MTMR14 in centronuclear myopathies and MTMR2 is mutated in the Charcot-Marie Tooth neuropathy

promote host cell survival and their subsequent dissemination (Pizarro-Cerda and Cossart 2004; Ramel et al. 2011). Other PIs species have been discussed in detail in other reviews (Di Paolo and De Camilli 2006; Itoh and Takenawa 2002; Lecompte et al. 2008; Martin 1998; Michell et al. 2006; Payrastre 2004).

Mammalian PI phosphatases are conserved through evolution and classified into two superfamilies: the protein tyrosine phosphatase and dual-specificity phosphatase (PTP/DSP) superfamily, and the inositide polyphosphate phosphatase superfamily. PI phosphatases of the PTP/DSP superfamily are metal-independent enzymes that exhibit the signature Cys-X5-Arg-Thr/Ser (CX5RT/S) in their active site implicated in the various chemical steps of the enzymatic reaction. First, the PO_3 moiety from the phosphoinositol headgroup is accepted by the nucleophilic cysteine residue to generate a phosphocysteine intermediate. The invariant arginine of the CX5RT/S motif stabilizes the transition-state, and the PO_3 moiety is transferred to a water molecule. Finally, a conserved aspartic acid, usually from an adjacent structural loop, completes the catalytic cycle by protonating the leaving oxygen and reconstituting an uncharged hydroxyl group on the PI that is released (Guan and Dixon 1991; Fauman and Saper 1996). The PI phosphatases of the PTP/DSP superfamily fall into four primary classes: the PI 4-phosphatases that either transform PtdIns(3,4)P_2 into PtdIns3P or PtdIns(4,5)P_2 to PtdIns5P; the PtdIns(3,4,5)P_3 3-phosphatase PTEN tumor suppressor; the PI 5-phosphatases like SHIP, synaptojanins, OCRL, or FIG4; and the myotubularin PtdIns3P and PtdIns(3,5)P_2 3-phosphatases (Chow et al. 2007; Gary et al. 2002; Maehama and Dixon 1998; Norris et al. 1997; Nystuen et al. 2001; Ungewickell et al. 2005). Here, we highlight the role of myotubularins in several cellular pathways, their implication in human diseases and discuss the potential pathological mechanisms.

The Myotubularin Phosphoinositides Phosphatases and Inactive Homologs

Myotubularins are only found in eukaryotes and define a large protein family highly conserved from yeast to human (Laporte et al. 1998; Lecompte et al. 2008). Humans express 14 myotubularin members distributed into 6 phylogenetic subgroups (Fig. 10.2a). Three subgroups have PI 3-phosphatase activity: MTM1 and the myotubularin-related (MTMR) proteins MTMR1 and MTMR2, MTMR3 and MTMR4, MTMR6 together with MTMR7 and MTMR8. The catalytically active myotubularins preferentially dephosphorylate PtdIns3P and PtdIns(3,5)P_2 and is one of the main pathways leading to PtdIns5P production (Blondeau et al. 2000; Chaussade et al. 2003; Taylor et al. 2000b; Tronchere et al. 2004). Noteworthy, the other three sub-groups contain naturally-occurring missense substitutions that involve the Cys and Arg residues of the canonical CX5R(S/T) motif and lack enzymatic activity: MTMR5 and MTMR13, MTMR9, MTMR10 with MTMR11 and MTMR12. In addition, the MTMR14 protein, also called JUMPY or egg-derive tyrosine phosphatase, has a similar CX5R(S/T) motif to myotubularins and share their substrate specificity; however, phylogenetic studies and protein domain composition suggested it defines a separated family (Lecompte et al. 2008; Tosch et al. 2006; Yamaguchi et al. 1999). The MTMR15 protein, once defined as part of

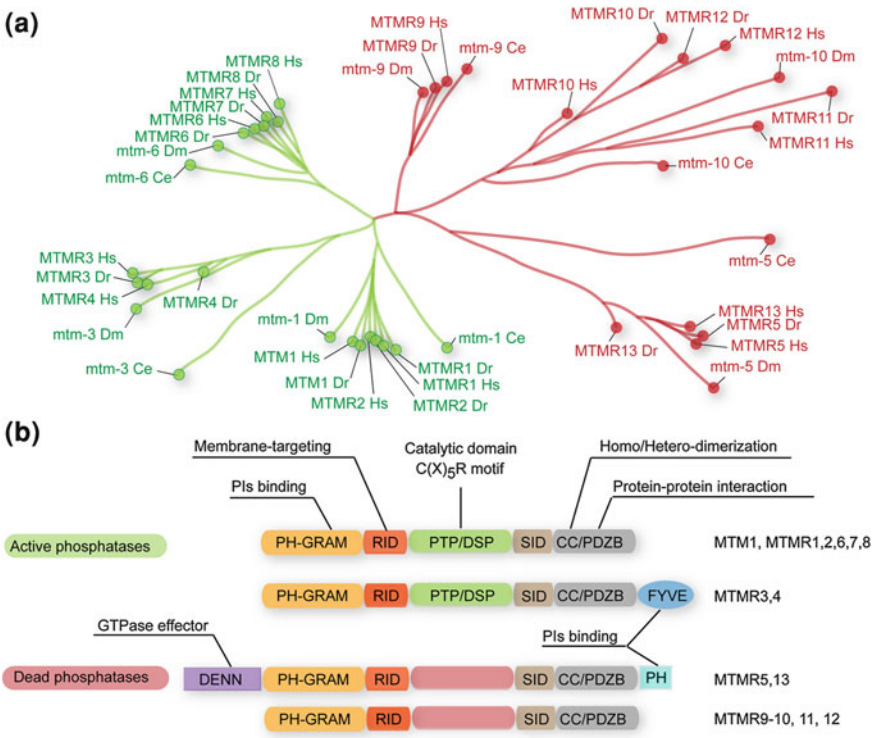

Fig. 10.2 Phylogenetic relationship and protein domains of active and inactive myotubularin phosphatases. (**a**) A phylogeny of myotubularins from human (*Homo sapiens*, *Hs*), zebrafish (*Danio rerio, Dr*), fruit fly (*Drosophila melanogaster, Dm*), and nematode (*Caenorhabditis elegans, Ce*). Catalytically active myotubularins are in green, catalytically inactive in red. Myotubularins were identified by using human sequences as queries for BLAST searches of the indicated genomes. The phylogenetic tree was adapted from Robinson and Dixon (2006). (**b**) Drawing of myotubularin domains and motifs in the human myotubularins. All myotubularins have a pleckstrin homology-glucosyltransferases rab-like GTPase activators and myotubularins (*PH-GRAM*), a rac-induced recruitment domain (*RID*), the protein tyrosine phosphatase/dual-specificity phosphatase (*PTP/DSP domain*), the set-interacting domain (*SID*) and a coiled-coil (*CC*) domain followed by a PDZ-binding motif (Postsynaptic Density-95, disks large and Zona occludens-1). Besides, MTMR3 and MTMR4 have a FYVE domain, while MTMR5 and MTMR13 contain DENN and PH domains

the myotubularin inactive members, does not share extensive homology with myotubularins and was renamed FAN1, a nuclease implicated in DNA repair (Alonso et al. 2004; Liu et al. 2010; Patzko and Shy 2011).

The so-called dead phosphatase myotubularins are probably not acting as substrate-traps but several studies converged to show that they unexpectedly heterodimerize with their active homologs (Kim et al. 2003; Mochizuki and Majerus 2003; Nandurkar et al. 2003). Doing so, they may either be critical for the localization of their active homolog, for appropriate presentation of the PI

substrate to the catalytically active subunit in a cellular context, or for a direct activation of its catalytic activity (Berger et al. 2006b; Taylor et al. 2000b; Zou et al. 2009). The dead phosphatases may thus indirectly regulate the phosphorylation status of PIs. This original regulation does not hold true for all species, as for example *Saccharomyces cerevisiae* expresses a single active MTM1 homolog in yeast (Ymr1), and the yeast genome does not encode for a dead-phosphatase myotubularin (Lecompte et al. 2008; Robinson and Dixon 2006). Homodimerization of myotubularins has also been reported, for example in the case of MTM1 where it could be triggered by PtdIns5*P* and induces an increase in enzymatic activity based on an allosteric mechanism (Schaletzky et al. 2003).

The domain structure common to myotubularins includes a Pleckstrin homology, glucosyltransferases, rab-like GTPase activators and myotubularins(PH-GRAM), a rac-induced recruitment (RID) domain also called MTMR domain (IPR010569 in Interpro database; http://wwwdev.ebi.ac.uk/interpro/), the PTP/DSP phosphatase-like domain, the set-interacting domain (SID) and a coiled-coil (CC) domain followed by a PDZ-binding motif (Fig. 10.2b). The GRAM domain, which overlaps with a PH motif, appears to bind to PIs although a more recent study did not confirm this affinity (Begley et al. 2003; Choudhury et al. 2006; Doerks et al. 2000; Tsujita et al. 2004). The RID is a membrane-targeting motif necessary for myotubularin recruitment to Rac1-induced membrane ruffles, whereas the SID and the PDZ-binding motif domain mediate protein–protein interactions (Bolino et al. 2004; Laporte et al. 2002; Previtali et al. 2003). The CC domain is critical for homo and/or hetero-dimerization of myotubularins, and the PH-GRAM has also been implicated in this process (Berger et al. 2003; Lorenzo et al. 2005; Nandurkar et al. 2003; Robinson and Dixon 2005). The MTMR3/4 and MTMR5/13 subclasses contain additional conserved modules, including FYVE, PH, and DENN domains (Robinson and Dixon 2006; Laporte et al. 2001). While the FYVE and PH domain are domains found to bind PtdIns3*P* and PIs in other proteins and sustain the implication of myotubularins in PIs regulation, the DENN domain is found in several Rab GTPase exchange factors, suggesting a role for MTMR5 and MTMR13 in Rab regulation (Yoshimura et al. 2010).

Studies in cultured cells showed that several myotubularins are associated to endosomal compartments and other intramembranes i.e. profiles consistent with involvements of these proteins in the control of PtdIns3*P* and PtdIns(3,5)P_2 signaling to regulate protein trafficking at the endosomal system. Indeed, PtdIns3*P* and PtdIns(3,5)P_2 are present on endosomal compartments where PtdIns3*P* predominates on early endosomes and PtdIns(3,5)P_2 on late endosomes (Cao et al. 2007, 2008; Laporte et al. 2002; Mochizuki and Majerus 2003; Zhao et al. 2001). Additional studies using yeasts supported a role of myotubularin in vesicle homeostasis (Blondeau et al. 2000; Taylor et al. 2000a).

Myotubularin-Related Diseases

Myotubularin (MTM1), the pioneer member of myotubularins, was discovered by positional cloning as the gene mutated in X-linked centronuclear myopathy (XLCNM) (Laporte et al. 1996). Later, MTMR2 and MTMR13 were found mutated in demyelinating Charcot-Marie-Tooth neuropathy types 4B1 and 4B2, respectively (Azzedine et al. 2003; Bolino et al. 2000; Senderek et al. 2003). In addition, several myotubularins have been recently linked to multifactorial diseases. Hence, the interest in myotubularins is stoked by their implication in human diseases.

X-Linked Centronuclear/Myotubular Myopathy

Mutations in the myotubularin (MTM1) gene on chromosome Xq28 have been identified in patients with the X-linked recessive form of centronuclear myopathy (XLCNM) , also called myotubular myopathy (XLCNM, OMIM 310400) (Laporte et al. 1996). XLCNM is resulting in a very severe and generalized muscle weakness and hypotonia, external ophthalmoplegia, and respiratory distress (Jungbluth et al. 2008). The disease incidence is about 1:50,000 in newborn males. Signs of antenatal onset comprise reduced fetal movements and polyhydramnios. Death occurs usually during the first year of life from respiratory failure, although a few milder cases were described to survive to adulthood (Herman et al. 1999). Mutations in the MTM1 gene have been now identified in more than 90 % of affected male patients and about 200 MTM1 mutations widespread through the gene have been reported so far (Laporte et al. 2000). On muscle biopsy, centronuclear myopathy (CNM) is characterized by centrally placed nuclei surrounded by a perinuclear halo devoid of myofilaments and occupied by mitochondrial and glycogen aggregates (Romero 2010). The characteristic central nuclei are seen in all muscles, including extraocular muscles, and may affect up to 90 % of fibers (Ringel et al. 1979; Romero 2010). Predominance of type I fibers was also frequently observed in muscle patients. Immunohistochemical studies have demonstrated consistent but nonspecific abnormalities: persistent fetal expression pattern of various proteins including the cell surface protein N-CAM, myosin, vimentin, and desmin have been reported in male infants with the X-linked form, but more recent immunohistochemical studies on sequential biopsies in long-term survivors suggest that the expression of developmentally regulated proteins eventually decreases as in healthy individuals (Dorchies et al. 2001; Fidzianska et al. 1994; Grainger et al. 2011; Misra et al. 1992; Van der Ven et al. 1995a; Yu et al. 2003). Other proteins abnormally expressed in XLCNM include laminin and collagen components (Van der Ven et al. 1995b). Observations in an *Mtm1*-null mouse model suggest a muscle-specific role of myotubularin in muscle fiber maintenance but not in myogenesis (Buj-Bello et al. 2002). A recent gene expression profiling study in muscles with different MTM1 mutations revealed upregulation of transcripts for cytoskeleton and extracellular matrix proteins, indicating that remodeling of cytoskeleton and extracellular

architecture plays a role in the atrophy and intracellular disorganization observed in XLCNM (Noguchi et al. 2005). Prolonged expression but eventual decrease of developmentally regulated proteins in muscle from affected infants suggests maturational delay rather than complete developmental arrest in this condition. Recent data in *Mtm1* knockout mice and zebrafish morphants suggested structural anomalies of the triad, a connection of one T-tubule and two sarcoplasmic reticulum saccules underlying the excitation–contraction (EC) coupling (Al-Qusairi et al. 2009; Dowling et al. 2009) (Fig. 10.3a). These morphological defects lead to disruption of EC-coupling machinery, which affects normal Ca2+ turnover and muscle contraction (Al-Qusairi et al. 2009). However, the precise localization and role of MTM1 in skeletal muscle remain to be determined. Interestingly, defects in triad structure have also been found in autosomal forms of centronuclear myopathies due to mutations in BIN1 (amphiphysin 2) and DNM2 (dynamin 2), both regulators of membrane remodeling and trafficking (Bitoun et al. 2005, 2007, 2009; Claeys et al. 2010; Nicot et al. 2007; Toussaint et al. 2011). Thus, an intriguing hypothesis is emerging of a common pathway involving MTM1, DMN2, and BIN1, which should function in the maintenance of the triad structure by regulating specialized membrane compartment and/or cytoskeleton rearrangement.

MTMR14/hJUMPY Implication in Centronuclear Myopathy

The MTMR14 gene is located on chromosome 3p25.3 and is conserved down to flesh flies and drosophila. It is expressed in different tissues and particularly at a high level in skeletal muscle and, as for *Mtm1*, *Mtmr14* expression level increases during myoblast differentiation to myotubes in vitro. MTMR14 is also able to efficiently dephosphorylate PtdIns3*P* and PtdIns(3,5)P_2 at position 3 of the inositol ring (Tosch et al. 2006) .

Screening of CNM patients with neonatal, childhood and adult onsets, without mutation in the MTM1 genes, revealed amino acid changes in MTMR14/JUMPY in two cases with early onset (Tosch et al. 2006). One patient had a heterozygous missense p.Arg336Glu. This 12-year-old boy had a neonatal hypotonia and hypoxia and a stable or slowly progressive disease with general hypotonia and diffuse weakness, affecting predominantly proximal portions of the limbs, together with ophthalmoparesis. The arginine at position 336 is conserved in all the MTMR14 protein orthologs and in all PTP/DSP phosphatases, as it is one of the amino acids required for the enzymatic activity in the CX5RT/S signature (Tosch et al. 2006). The second patient had a non-conservative heterozygous p.Tyr462Cys missense variation. This 36-year-old female had a neonatal hypotonia followed by a stable muscle involvement and also presented ophthalmoparesis. The tyrosine 462 lies outside the PTP/DSP domain and is conserved at least in mammals and birds. Importantly, the p.Arg336Glu variant and, to a lesser extent, the p.Tyr462Cys variant impaired the enzymatic activity of MTMR14. One of the patients also had a mutation in the *DNM2* gene, suggesting that MTMR14 defect may modulate the phenotype due to the *DNM2* mutation but not directly induces CNM.

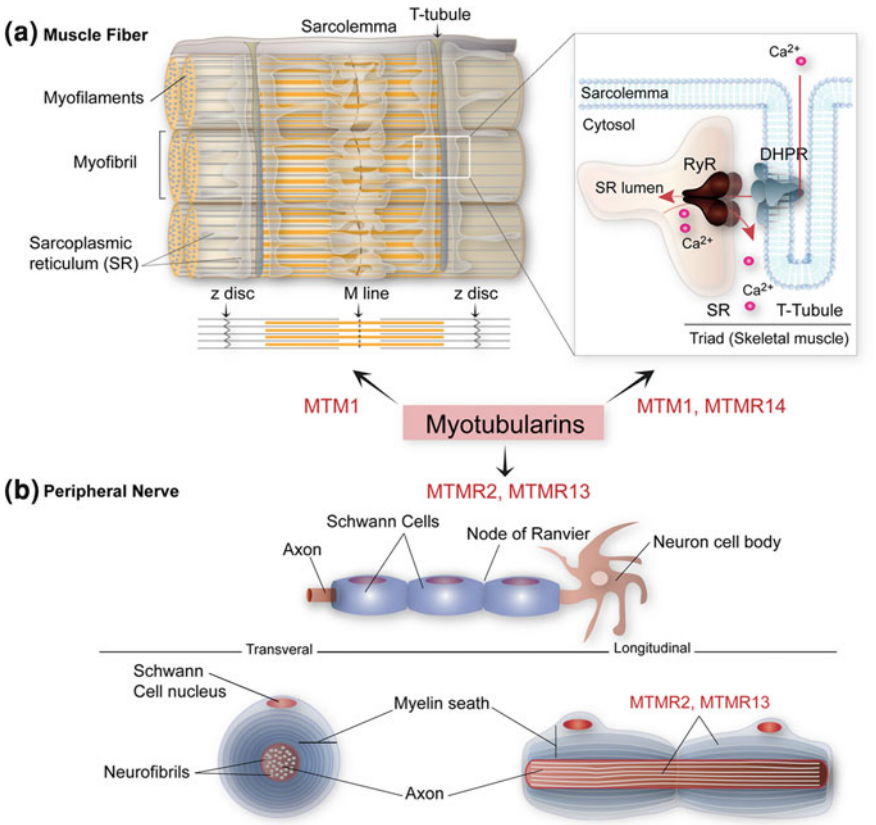

Fig. 10.3 Tissue-specific role of myotubularins and pathological relevance. (**a**) MTM1 and MTMR14 are implicated in centronuclear myopathies (X-linked form and sporadic cases, respectively). Both proteins are implicated in skeletal muscle maintenance and Ca2+ homeostasis. The latter mechanism involves the Ca2+ entry from the extracellular space via the transmembrane channel complex DHPR while a second channel, the Ryanodine receptor (*RyR1*) on the internal compartment storage called the sarcoplasmic reticulum (*SR*), is in charge of the fine regulation of the cytoplasmic level of Ca2+ (*squared*). In centronuclear myopathies involving MTM1 and MTMR14, defects in the triad (junction between two sarcoplasmic reticulum and one T-tubule) was observed, paralleling defects in RyR1 function. (**b**) Both MTMR2 and MTMR13 have been associated to Charcot-Marie-Tooth neuropathies (CMT4B1 and CMT4B2, respectively) characterized by myelin outfoldings. Myelin in the peripheral nervous system is generated and maintained by myelinating Schwann cells. This highly specialized cell type enwraps segments of axons with multiple layers of its plasma membrane, and segments are connected through nodes of Ranvier. MTMR2 and MTMR13 can form a heterodimer and MTMR13 could regulate MTMR2 phosphatase activity in vitro suggesting an important role of the MTMR2/MTMR13 complex in CMT physiopathology

Vergne et al. reported a role for MTMR14/JUMPY in the regulation of autophagy. They discovered that MTMR14 associated with early autophagosomes and negatively regulated progression through the steps of autophagy (Vergne et al. 2009).

Knockdown of *MTMR14* in cultured cells resulted in increased autophagy, whereas overexpression inhibited this process. MTMR14 phosphatase activity was required for its role as a regulator of autophagy, a finding consistent with the known importance of PtdIns3*P* in the promotion of the early steps of autophagy (Vergne et al. 2009). In agreement, an increase in lipidated LC3 was noted in *Mtmr14* KO mouse muscle and in muscles from *Mtmr14* zebrafish morphants (Dowling et al. 2010; Hnia et al. 2011a). Shen et al. (2009) reported on mice with a targeted deletion in *Mtmr14* that resulted in a mild phenotype of early onset exercise intolerance and late-onset muscle wasting. They also observed a reduction in force production in muscle from the knockout animals, and demonstrated that this change was associated with calcium leakage from the sarcoplasmic reticulum. These changes in calcium homeostasis were most probably due to a direct activation of the skeletal muscle ryanodine receptor (RYR1) by excess of PtdIns(3,5)P_2 (Shen et al. 2009). Similarly, morpholino-based experiments in zebrafish suggested that MTMR14 is important for excitation—contraction coupling as morphants failed to respond to high-frequency electrical stimulation (Dowling et al. 2010). In both zebrafish and mice, downregulation or deletion of MTMR14 did not reproduce the centralization of nuclei observed in patients with CNM; however, structural defects of the triad were observed by electron microscopy (Dowling et al. 2010; Hnia et al. 2011a). Moreover, decreased *Mtmr14* in an *Mtm1* knockdown background potentiated the CNM-like phenotype in zebrafish. As defect in calcium homeostasis and structural anomalies of the triads were also reported as common signs of different forms of centronuclear myopathies, it suggests that MTMR14 impairment is associated to muscle weakness in such diseases (Toussaint et al. 2011).

Charcot-Marie-Tooth Peripheral Neuropathies Type 4B

Charcot-Marie-Tooth disease (CMT) denotes a heterogeneous group of genetic diseases that affect peripheral nerves, leading to pronounced muscular atrophy and weakness of distal limbs. Electrophysiological and neuropathological data differentiate sensory and motor neuropathies. In some classes, only motor or sensory neurons might be affected, and in others, both cell types may be involved. Thus, axonal CMT2 diseases can be dominant or recessive, and similarly demyelinating CMT are classified depending on their inheritance: CMT1 for dominant and CMT4 for autosomal recessive. The intermediate forms are mainly following a dominant inheritance (DI-CMT) or X-linked inheritance (CMTX) (Patzko and Shy 2011). Nerve conduction velocity (NCV) measurements are used to differentiate between demyelinating and axonal forms: uniformly slow NCV less than 38 m/s in the arms is characteristic of demyelinating CMT. Intermediate CMT have NCV values in the range 25–45 m/s.

Autosomal recessive forms of demyelinating CMT are collectively designated CMT4 and focally folded myelin sheaths around peripheral nerves are characteristic of CMT4B sub-type (Dubourg et al. 2006; Gambardella et al. 1997; Zappia et al. 1997). Myelin in the peripheral nervous system is generated and maintained

by myelinating Schwann cells. This highly specialized cell type enwraps segments of axons with multiple layers of its plasma membrane, and segments are connected through nodes of Ranvier. MTMR2 was found mutated in CMT4B (CMT4B1, OMIM 601382) (Bolino et al. 2000). Mutations in the MTMR13/SBF2 gene, which encodes a catalytically inactive member of the myotubularin family, cause CMT4B2 (OMIM 604563), which has almost similar pathological features to CMT4B1 (Azzedine et al. 2003; Senderek et al. 2003). MTMR2 and MTMR13 can form heterotetramers and MTMR13 could regulate MTMR2 phosphatase activity in vitro (Berger et al. 2006b; Robinson and Dixon 2005). The implication of both proteins in similar disease was the first proof that myotubularin heterodimerization has important roles at the physiological level. However, it remains an open question how their interaction could impact on the physiopathology of CMT4B1 and CMT4B2. MTMR2 and MTMR13 deficiency exclusively in Schwann cells in mouse models is sufficient to generate myelin outfoldings as seen in CMT4B1 and CMT4B2 (Bonneick et al. 2005; Robinson et al. 2008; Tersar et al. 2007). Such aberrant structures contain redundant myelin membranes that originate during late development of myelinating Schwann cells mainly at the paranodes and Schmidt-Lanterman incisures, regions that contain Schwann cell cytoplasm and intracellular organelles such as endosomes and lysosomes (Fig. 10.3b). Paranodes and Schmidt-Lanterman incisures are also thought to be the main regions of the myelin sheath where addition and turnover of myelin membranes and its protein components occur. These findings, together with the known functions of the PI substrates of MTMR2 on intramembranes suggest that MTMR2/MTMR13 couple could be involved somehow in the regulation of membrane addition and/or remodeling. Altered membrane trafficking, recycling, or impaired degradation may lead to the observed phenotype. Noteworthy, other genes mutated in different forms of demyelinating CMT encode proteins implicated in endosome/lysosome function like FIG4, a PtdIns(3,5)P_2 phosphatase, and LITAF, an integral membrane protein of lysosome and late endosome (Patzko and Shy 2011; Zhang et al. 1997). Indeed, recent elegant crosses in mice by Vaccari and colleagues have shown a genetic interaction between MTMR2 and FIG4 both in Schwann cells and neurons (Vaccari et al. 2011). In addition, reduction of FIG4 rescued *Mtmr2*-null myelin outfoldings in vitro and in vivo, suggesting some possible therapeutic approaches and supporting that PIs misregulation is a cause of CMT4 neuropathies.

Potential Link between Myotubularins and Multifactorial Diseases

Cancer: Over the past 2 decades, PI effectors and several metabolizing enzymes have been investigated in cancer. In particular, PTEN has blossomed into one of the featured molecules in cancer biology. Hundreds of published reports focused on PTEN structure, function, and mutations in the context of various human diseases. After P53, PTEN is the most commonly mutated gene in human cancer, and the most deleted/mutated phosphatase in human sporadic and hereditary

cancer syndromes (Liaw et al. 1997; Nelen et al. 1997; Stiles et al. 2004; Suzuki et al. 2009). More recently, alteration of several other PTPs/DSPs has been implicated in oncogenic transformation (Wang et al. 2004). By analyzing a public genomic database, a recent study reported several MTMR3 mutations in colorectal and gastric cancers (Song et al. 2010). MTMR3 genomic region is also linked to lung cancer susceptibility (Hu et al. 2011). The suspected role of MTMR3 in autophagy might be linked to the pathology, although a direct link remains to be found (Taguchi-Atarashi et al. 2010). In addition, expression of the dead phosphatase MTMR11 is also altered following modulation of the oncogene HER2 in cells, suggesting a potential link between myotubularins and oncogenic program in cancer (Lucci et al. 2010).

Epilepsy: Generalized epilepsy with febrile seizures plus ($GEFS^+$) is a familial condition in which patients have febrile seizures variably associated with epilepsy. Febrile seizures are the most common convulsive event in humans, affecting 2–5 % of children. The $GEFS^+$ context is inherited as an autosomal dominant trait with incomplete penetrance. It is genetically heterogeneous and several ion channel genes have been implicated in $GEFS^+$. Recently, a sixth locus for $GEFS^+$ was identified on chromosome 8p23-p21 (Baulac et al. 2008). No ion channel genes are located in this interval. Two of the candidate genes located in the genetic interval are MTMR7 and MTMR9, although no mutations have been identified in these genes yet. The identification of the responsible gene will probably uncover a new mechanism of pathogenesis for $GEFS^+$.

Obesity: Obesity is a genetically heterogeneous disorder and its genetic susceptibility is likely to differ among various ethnic groups. Common obesity arises when an individual's genetic background is susceptible to an environment that promotes energy intake over energy expenditure. Many cases of monogenic obesity (obesity associated with a single-gene mutation) have been reported. Most of the genes causing monogenic obesity are expressed in the hypothalamus and have been indicated to have important roles in the regulation of food intake; therefore, genes expressed in the hypothalamus are likely to be good candidates for susceptibility to obesity. Recent reports, performed through an association studies using a large number of gene-based SNPs, have reported that the MTMR protein-9 (MTMR9) gene is associated with obesity (Hotta et al. 2011; Yanagiya et al. 2007). MTMR9 is expressed in the lateral hypothalamic area, paraventricular nucleus and accurate nucleus of the hypothalamus, the center for food intake regulation, and MTMR9 expression was regulated by diet. These data suggest that MTMR9 is likely to contribute to genetic susceptibility to obesity.

Connecting Molecular Pathways and Physiopathology in Myotubularinopathies

Phosphoinositide Metabolism and Membrane Trafficking

The myotubularin PI 3-phosphatase family has been partially explored in vitro and ex vivo. As for MTMR2, MTM1 was proposed to bind to PtdIns(3,5)P_2 through the N-terminal PH-GRAM domain (Berger et al. 2003; Tsujita et al. 2004). MTM1 and MTMR2 localizes to early and late endosomal compartments, respectively, where PtdIns3*P* and PtdIns(3,5)P_2 are particularly enriched (Cao et al. 2007, 2008). Overexpression of MTM1 in cultured cells altered the trafficking of EGF receptor from the late endosome to lysosome and subsequently its degradation. However, the PH-GRAM domain was not mediating membrane localization, as mutations in this domain did not affect MTM1 endosomal localization. The role of the PH-GRAM domain of several myotubularins is likely to mediate their PtdIns3*P*/PtdIns5*P*-dependent oligomerization and a PtdIns5*P*-specific activation rather than targeting the concerned myotubularin in specific compartments. Indeed, addition of PtdIns5*P* to a catalytically inactive mutant of MTM1 induced its oligomerization as a heptameric ring (Schaletzky et al. 2003). Cao et al. (2007) proposed that activated Rab5 and Rab7 bind to P150 (VPS15), the regulatory subunit of PI 3-kinase class III (VPS34) leading to activation of VPS34, elevation of PtdIns3*P* and recruitment of EEA1 and Hrs effectors on early and late endosomes, respectively. The subsequent interaction of MTM1 with p150 should then lead to a decrease of PtdIns3*P* levels and a decreased level of EEA1 and Hrs on endosomes. Such tripartite complex, consisting of a PI kinase, a PI phosphatase and a regulatory protein, may also exist for other PI transformation reactions controlling the level of PtdIns5*P* and PtdIns(3,5)P_2 (Lecompte et al. 2008).

Similarly, using HEK293 cells, Franklin et al. have shown a localization of MTMR2 at endosomes (Franklin et al. 2011). They reported that MTMR2, not phosphorylated at residue Ser58, co-localized with Rab5 on early endosomes, where it depleted pools of PtdIns3*P* in response to extracellular stimuli likely activating serine phosphatases. Conversely, when Ser58 is phosphorylated in steady-state conditions, MTMR2 preferentially localizes in the cytosol where it would probably not access any PI pools. In addition, downregulation of MTMR2 mRNA in A431 cells has been shown to alter EGF receptor trafficking at the level of late endosome/lysosomes, where MTMR2 has been proposed to function in complex with P150 and Rab7 (Cao et al. 2008). Moreover, the increase of PtdIns(3,5)P_2 levels upon hypo-osmotic shock in COS7 cells led to the recruitment of MTMR2 at membranes of vacuoles formed under these conditions (Berger et al. 2006b). Berger et al. showed that membrane association of MTMR2 in hypo-osmotic condition requires both PH-GRAM and coiled coil domains and does not depend on phosphatase activity. However, unlike MTM1, MTMR2 vacuolar localization is dependent on its PH-GRAM domain underlying differential PI-dependent regulatory mechanisms within the myotubularin family.

Drosophila *mtm*, the ortholog of both human MTM1 and MTMR2, acts on a sub-pool of PtdIns3*P* generated by the class II PI 3-kinase (Pi3K68D), likely at the plasma membrane or on early endosomes (Velichkova et al. 2010). Velichkova et al. elegantly showed that, by controlling this PtdIns3*P* sub-pool, *mtm* regulates cortical remodeling, downregulates endosomal influx and promotes membrane efflux, thus maintaining endosomal homeostasis in the endolysosomal axis. By performing in vivo studies on *mtm* mutants, the same authors also reported that *mtm* is required for integrin-mediated myofiber attachment (Ribeiro et al. 2011). *Mtm* depletion increased integrin turnover at the sarcolemma, an accumulation of integrin on PtdIns3*P* enriched endosomes and disruption of T-tubules. Depletion of Pi3K68D rescued integrin accumulation, thus revealing the existence of a pathway that controls integrin recycling in muscle. However, Pi3K68D depletion did not rescue the defect of T-tubules caused by *mtm* deplection, suggesting a distinct Pi3K68D-dependent and PI-dependent and independent *mtm* functions in muscle. Similar defects in integrin localization and T-tubule disruption were also observed in XLCNM biopsies, thus supporting a role for integrin adhesion and triad maintenance in the pathogenesis of the XLCNM (Ribeiro et al. 2011; Toussaint et al. 2011). Furthermore, ectopic overexpression of MTM1 by adeno-associated-virus (AAV) in wild type skeletal muscle lead to membrane stacks accumulation at subsarcolemmal regions, suggesting that depletion or/and over-production of the MTM1 PIs substrates and products is likely to affects membrane formation and remodeling in muscle cells (Buj-Bello et al. 2008).

Similarly, MTMR2 acts on membrane homeostasis. *Mtmr2*-null nerves showed myelin outfoldings, which can be considered as a model of impaired membrane formation preferentially arising at nodal/paranodal regions, known sites of membrane remodeling (Dang et al. 2004). MTMR2 has been shown to interact with the Dlg1 (disks large 1)/synapse associated 97 (SAP97) scaffolding protein, which is involved in polarized membrane trafficking and membrane addition (Bolino et al. 2004). Interestingly, Dlg1 localization is altered at paranodal regions in *Mtmr2*-null peripheral nerves, suggesting that the MTMR2/Dlg1 complex might be relevant for the CMT4B1 pathogenesis (Bolino et al. 2004; Bolis et al. 2005). Bolis et al. (2009) have reported Dlg1 interaction with kinesin 13B (kif13B) and sec8, which are involved in vesicle transport and membrane tethering in polarized cells, respectively. They proposed that the interaction of Dlg1 with Sec8 promotes membrane formation whereas *Mtmr2* negatively regulates membrane addition through its interaction with Dlg1. Defects in MTMR2/Dlg1-mediated control of membrane formation during Schwann cell myelination might lead to excessive myelin with redundant folds (Bolis et al. 2009). The role of MTMR2 in the regulation of endocytic trafficking might be physiologically more relevant in specialized cell types as for example in neurons. Recently, downregulation of *Mtmr2* mRNA in cultured hippocampus neurons suggested that MTMR2, through PSD95 interaction, might downregulate endocytic events important for spine maintenance (Gambardella et al. 1997; Lee et al. 2010).

Interactors and Tissue-specific Regulation

While myotubularins appear rather ubiquitously expressed, mutations in several of them lead to diseases affecting different and specific tissues. Thus, there should be some tissue-specific regulatory mechanisms that could be mediated by the type of extracellular stimuli, specificity of PIs turnover in different cell types, or specific interactors. This hypothesis is supported by the recent discovery of interactors for specific myotubularins.

Initially, in vitro studies suggesting that a myotubularin could form a heterodimer with another member within the same family have supported that such regulation could have a major role in the cellular function of myotubularins. Such molecular configuration implicated an active/dead-phosphatase couple of myotubularins. Specific heterodimers exist, although all possibilities were not investigated yet, and such specificity may sustain tissue-targeted functions of myotubularins (Lorenzo et al. 2005). The best characterized heterodimers are MTM1 with MTMR12, MTMR2 with MTMR5 or MTMR13, and MTMR9 with MTMR6 or MTMR7 (Azzedine et al. 2003; Kim et al. 2003; Mochizuki and Majerus 2003; Robinson and Dixon 2005; Taylor et al. 2000b). A first example is the complex between MTM1 and MTMR12 (3-PAP: 3-phosphatase associated protein). The MTM1-MTMR12 heterodimer was biochemically discovered before the identification of the first myotubularin gene sequence as a protein complex with PtdIns3*P* phosphatase activity purified from rat brain extracts (Caldwell et al. 1991). Subsequent sequencing of this protein complex matched the discovered myotubularins and also suggested a role in human platelets (Nandurkar et al. 2001, 2003). Overexpressed MTM1 localized to the plasma membrane, causing extensive filopodia formation (Laporte et al. 2002). Co-expression of MTMR12 with MTM1 led to attenuation of filopodia formation and relocalization of MTM1 to the cytosol, toward the localization of MTMR12 (Nandurkar et al. 2003). This indicates that MTMR12 functions as an "adapter" for MTM1, regulating its intracellular location and thereby altering the phenotype resulting from MTM1 overexpression. MTMR12, and more generally dead-phosphatase myotubularins, may thus direct the enzymatically active myotubularins to specific PI pools.

MTMR2 interacts with MTMR5, another catalytically inactive myotubularin via its CC domain and mutations in the CC domain of either MTMR2 or MTMR5 abrogate this interaction. Through this interaction, MTMR5 increased the enzymatic activity of MTMR2 and modulated its subcellular localization (Kim et al. 2003). In addition, MTMR2 binds to MTMR13 (Sbf2), and both proteins are mutated in CMT4B (Previtali et al. 2003). MTMR2 homodimers interacted with MTMR13 homodimers to form tetrameric complexes (Berger et al. 2006a; Robinson and Dixon 2005). This association dramatically increased the enzymatic activity of MTMR2 toward PtdIns3*P* and PtdIns(3,5)P_2. MTMR2 and MTMR13 are mostly co-localized in the cytoplasm when exogenously expressed in cells. On membranes of large vesicles formed under hypo-osmotic conditions, MTMR13 favorably competed with MTMR2 for binding sites. These observations suggested that MTMR2 activity is tightly regulated, being high in the complex, moderate if

MTMR2 is not associated with MTMR13 or functionally blocked through competition with MTMR13 for membrane-binding sites (Berger et al. 2006b; Robinson and Dixon 2005). Given the fact that MTMR2/MTMR13 are interaction partners in Schwann cells in vitro and in vivo (Berger et al. 2006a), defect in this interaction is most likely the primary cause for the similar phenotypes observed in CMT4B1 and CMT4B2, indicating that these proteins act in concert in a common pathway essential for myelin maintenance.

The dead phosphatase MTMR9 interacts with MTMR6 and with MTMR7 (Mochizuki and Majerus 2003; Zou et al. 2009). MTMR9 binding increased the binding of MTMR6 to PIs and its catalytic activity. Moreover, co-expression of MTMR6 with MTMR9 decreased etoposide-induced apoptosis, suggesting that formation of this heterodimer has important cellular impact.

An unexpected link between MTM1/MTMR2 and intermediate filaments was reported. Intermediate filaments are important structural components of living cells and are essential for normal tissue structure and function; they provide physical resilience for cells to withstand the mechanical stresses of the host tissue (Herrmann et al. 2009). The Neurofilament light chain protein (NF-L), mutated in CMT disease including axonal, intermediate, and demyelinating forms, was found to interact with MTMR2 (Liem and Messing 2009; Previtali et al. 2003; Szaro and Strong 2010). Myelin outfoldings are due to loss of MTMR2 in Schwann cells, since conditional ablation in mice of *Mtmr2* in Schwann cells is both sufficient and necessary to provoke the myelin defect hallmark of CMT4B1 (Bolis et al. 2005). In the peripheral nervous system, NF-L is expressed mainly in neurons, whereas Schwann cells express NF-L mRNA only upon damage. Thus, it is likely that the MTMR2 and NF-L interaction is physiologically relevant in neurons, but the functional insight of this partnership and its impact on the physiopathology of CMT4B1 is not yet identified.

The second example is the interaction of MTM1 with the type III intermediate filaments, desmin, a muscle-specific protein (Hnia et al. 2011b). MTM1 bound directly to desmin and regulated filament assembly and architecture independently of its enzymatic activity, suggesting a crucial role for MTM1 in the regulation of the desmin network in skeletal muscle. Knockout or knockdown of MTM1 expression and disruption of the MTM1-desmin complex promoted desmin aggregation. Both MTM1 and desmin are implicated in muscle disorders and desmin mutations are associated with myofibrillar myopathies and cardiomyopathies (DRM, Desmin Related Myopathies, and DRCM, Desmin Related Cardiomyopathies). XLCNM mutations as well as DRM mutations abolished MTM1/desmin interaction and could not re-establish normal intermediate filaments network in *Mtm1* KO muscle cells. Accordingly, these data suggested a common pathophysiological mechanism between centronuclear and myofibrillar myopathies and underlined the importance of myotubularins in the regulation of intermediate filaments in different tissues (Hnia et al. 2011b). In addition, MTM1/desmin complex was found in the mitochondrial fraction and MTM1 depletion from muscle cells affected mitochondrial dynamics and function. These effects appeared both dependent and independent of desmin interaction as several MTM1 mutations, particularly those affecting

enzymatic activity, did not interfere with desmin interaction but affected mitochondrial dynamics (Hnia et al. 2011b). In zebrafish *mtm1* morphant muscles, the presence of dysmorphic and swollen mitochondria in the perinuclear region also supported the link between MTM1 and mitochondrial homeostasis (Dowling et al. 2009). Indeed, mitochondrial collapse around central nuclei is a sign of XLCNM found on muscle biopsies from affected patients (Romero 2010).

Concluding Remarks and Future Directions

Myotubularins have raised a high interest since the discovery of their implication in human diseases. In addition to that consideration, myotubularins appear as key players in the PIs metabolism. Although the lipid phosphatase activity of myotubularins was largely investigated in vitro and ex vivo, little is known about its importance in vivo. How and in which biological context the PI-related function of myotubularins is required will be an important query in the future. One may wonder why there are so many myotubularins in higher eukaryotes, most of them being rather ubiquitously expressed. The growing data obtained during the last few years support the idea that myotubularins functions are differentially regulated from one tissue to another. The emergence of newly identified protein partners supports the hypothesis that myotubularins regulate different PIs subpools in tissues and that they also have phosphatase independent functions. Recent finding using cell and animal models suggested that these PI phosphatases can also regulate many processes including cell proliferation and differentiation, survival, autophagy, cytokinesis, cytoskeletal, and cell junction dynamics. How myotubularins regulate these processes is barely understood, and whether defects in these pathways are primary causes of the "myotubularinopathies" remains to be investigated.

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