J Mol Med (2010) 88:339–350
DOI 10.1007/s00109-009-0587-4

REVIEW

Dynamin 2 and human diseases

Anne-Cécile Durieux · Bernard Prudhon · Pascale Guicheney · Marc Bitoun

Received: 2 November 2009 / Revised: 21 December 2009 / Accepted: 25 December 2009 / Published online: 3 February 2010

Abstract Dynamin 2 (DNM2) mutations cause autosomal dominant centronuclear myopathy, a rare form of congenital myopathy, and intermediate and axonal forms of Charcot–Marie-Tooth disease, a peripheral neuropathy. DNM2 is a large GTPase mainly involved in membrane trafficking through its function in the formation and release of nascent vesicles from biological membranes. DNM2 participates in clathrin-dependent and clathrin-independent endocytosis and intracellular membrane trafficking (from endosomes and Golgi apparatus). Recent studies have also implicated DNM2 in exocytosis. DNM2 belongs to the machinery responsible for the formation of vesicles and regulates the cytoskeleton providing intracellular vesicle transport. In addition, DNM2 tightly interacts with and is involved in the regulation of actin and microtubule networks, independent from membrane trafficking processes. We summarize here the molecular, biochemical, and functional data on DNM2 and discuss the possible pathophysiological mechanisms via which DNM2 mutations can lead to two distinct neuromuscular disorders.

Keywords Dynamin 2 · Centronuclear myopathy · Charcot–Marie-Tooth neuropathy · Endocytosis · Cytoskeleton · Monogenic disease · Biology

Abbreviations

PI4,5P2	phophatidylinositol 4,5-bisphosphate
PI3,4,5P3	phophatidylinositol 3,4,5-triphosphate
PI3,4P2	phophatidylinositol 3,4-bisphosphate
PI4P	phophatidylinositol 4-monophosphate
PI3P	phophatidylinositol 3-monophosphate
LPA	lysophosphatidic acid
GLUT4	glucose transporter 4
TGN	trans-Golgi network
BAR	Bin1/Amphiphysin/RVS167

A.-C. Durieux · B. Prudhon · M. Bitoun (✉)
Inserm, UMR S974, Institut de Myologie,
Groupe Hospitalier Pitié-Salpêtrière,
Paris F-75013, France
e-mail: m.bitoun@institut-myologie.org

A.-C. Durieux · B. Prudhon · P. Guicheney · M. Bitoun
UPMC Univ Paris 06,
IFR14,
Paris 75013, France

P. Guicheney
Inserm, UMR S956, Groupe Hospitalier Pitié-Salpêtrière,
Paris 75013, France

M. Bitoun
UMR_S974, Institut de Myologie,
Groupe Hospitalier Pitié-Salpêtrière,
75013 Paris, France

Dynamin 2 (DNM2) belongs to a superfamily of large GTPases, including three classical dynamins and several dynamin-like proteins, which are involved in a wide range of cell functions [1]. The importance of DNM2 was emphasized in 2005 with the demonstration of *DNM2* gene mutations causing two distinct human diseases [2, 3]. Our purpose is to review the molecular and functional data on DNM2 to highlight the pathophysiological hypotheses in DNM2-related diseases. Knowledge of the dynamins mainly comes from studies of the neuronal dynamin 1 (DNM1). However, we have focused this review on DNM2 since several studies have demonstrated notable differences between DNM1 and DNM2 [4–7].

DNM2 gene organization and isoforms

DNM2, one of three classical dynamins, was identified in rat liver and brain cDNA libraries [4, 8]. A human homologue was thereafter identified by screening of a fibroblast library [9]. The human transcript (3.6 kilobases) is ubiquitously expressed, with higher abundance in heart and skeletal muscle [9]. Human DNM2 is encoded by the *DNM2* gene located on the short arm of chromosome 19 (19p13.2). The gene is composed of 22 exons in a 114-kilobase region. Four major isoforms are expressed by the *DNM2* gene using a combination of two alternative splice sites (Fig. 1a). Exons 10 and 10bis have the same length (139 base pairs encoding the amino acids 399–445 in the middle domain) and are alternatively spliced. In addition, the exon 13bis (12-base pair length) can be spliced leading to the translation of proteins of 866 or 870 amino acids (Fig. 1) without or with the GEIL sequence at position 516–519 in the C-terminal part of the middle domain (MD). The four major isoforms have been shown to be expressed in a panel of rat tissues including brain, heart, kidney, liver, lung, pancreas, and testis [10]. The human tissue expression pattern is unknown, but we have shown expression of the four isoforms in skeletal muscle and peripheral nerve [11].

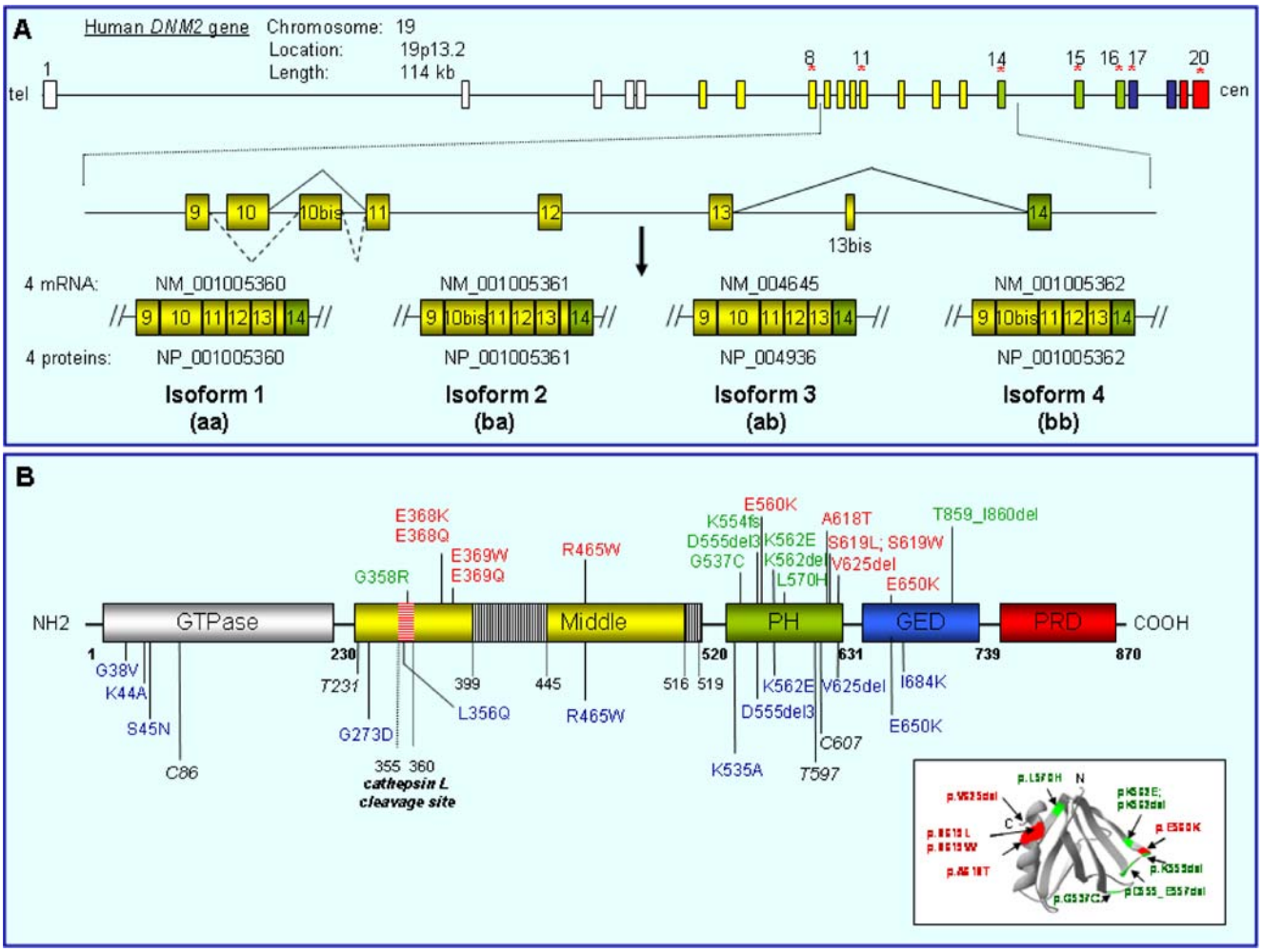

Fig. 1 *DNM2* gene organization and mutations. **a** Schematic organization of the human DNM2 gene showing alternative splicing. *Asterisks* indicate the seven exons in which disease-associated mutations have been identified. Exons were *colored* relative to the encoded protein domain illustrated in **(b)**. The combination of the two alternative splice sites leads to the translation of four DNM2 isoforms. Isoforms 1, 2, 3, and 4 are also known as isoforms aa, ba, ab, and bb, respectively. **b** Schematic representation of DNM2 showing the five protein domains and the position of the 19 disease-associated mutations. CMT-mutations are indicated in *green* and CNM-mutations in *red*. The two regions of variation (at positions 399-445 and 516-519) between the four isoforms were indicated in the MD by *black lines*. In *black* are indicated the sites of post-translational modifications (phosphorylation, nitrosylation, and cathepsin L cleavage). The CMT-mutation G358R is located in the cathepsin L cleavage site. In *blue* are indicated the DNM2 constructs with point mutations or small deletions overexpressed in vitro [60]. *Insert in* **b**: Position of the CNM- and CMT-mutations on the 3D structure of the PH domain (accession number 63660 in the NCBI 3D structure database). The N-terminal part of the domain, bearing CMT-mutations and only one CNM mutation, is composed of β-sheets involved in the interaction with membrane phosphoinositides

Specific functions of these isoforms will be discussed below.

DNM2 structure and regulation

The 98 kDa DNM2 is a large GTPase composed of a N-terminal GTPase domain, an MD, a pleckstrin homology domain (PH), a GTPase effector domain (GED), and a C-terminal proline rich domain (PRD; Fig. 1b). The catalytic GTPase domain is responsible for GTP binding and hydrolysis, whereas the MD is involved in DNM2 self-assembly [12] and in GTP hydrolysis-induced conformational change of the protein [13]. The PH domain interacts with membrane phosphoinositides and therefore is involved in the targeting of dynamin to membranes [14]. The DNM2-PH domain displays phosphoinositide binding affinity following the order: PI4,5P2≈PI3,4,5P3≈PI3,4P2>PI4P≈PI3P, and DNM2 oligomerization appears crucial for high affinity [15]. The GED probably participates in the self-assembly of DNM2 and acts as a GTPase-activating protein [16]. The PRD contains multiple Src homology 3 (SH3) binding motifs and mediates multiple protein–protein interactions (Table 1). A general model of dynamin intramolecular interaction was proposed, in which the GTPase domain, MD and GED interact to drive self-assembly and the PH domain mediates interaction with membrane lipids [1].

In vitro at high ionic strength, DNM2 is in monomer–tetramer equilibrium. At low ionic strength, DNM2 self-assembles into higher-order aggregates leading to a drastic increase in GTPase activity [17, 18]. Microtubules or phospholipid vesicles, especially those containing PI4,5P2, also induce self-assembly and increase DNM2 GTPase activity [5, 17, 19]. Purified from baculovirus, GTP-bound and GDP-bound monomer DNM2 has Kd values of 13.2 and 7.1 μM, respectively, with GTPase activity of 37 nmol/mg/min. When in an oligomeric state, the GTPase activity of DNM2 markedly increased and Kd values decreased [20]. When compared with small GTPases, DNM2 exhibits a relatively low affinity for GTP (Km=12 μM) but high intrinsic rates of GTP hydrolysis.

DNM2 activity is regulated by post-translational modifications. DNM2 becomes phosphorylated on Tyr231 (MD) and Tyr597 (PH domain) through Src-mediated phosphorylation, leading to albumin endocytosis [21]. In contrast, dopamine leads to the dephosphorylation of DNM2 by increasing protein phosphatase 2A activity, necessary for dopamine-induced Na^+K^+-ATPase endocytosis [22]. *S*-nitrosylation of Cys86 (GTPase domain) and Cys607 (PH domain) by nitric oxide (NO) increases GTPase activity and endocytosis [23]. In a mouse model of kidney disease, cathepsin L induction leads to the cleavage of the cytoplasmic DNM2 at positions 355–360 (Fig. 1b) [24]. Sever et al. identified a cathepsin L cleavage site at positions 355–360 in the middle domain (Fig. 1b). Actin network is then reorganized in renal podocytes leading to filtration impairment and proteinuria [24]. It remains to be determined whether such proteolytic regulation occurs only in pathological context and in other tissues. Finally, it was demonstrated that Ca^{2+} inhibits DNM2 GTPase activity (IC_{50}=150 μM) and receptor-mediated endocytosis in Hela cells [25]. This may have physiological importance in excitable cells like neurons and muscle fibers.

It is still largely unknown how DMN2 expression is regulated. In rat, DNM2 is up-regulated during normal pancreatic development after birth [26] but not in the liver [8] or the brain [27]. In mouse, treatment with opioid agonist results in increased DNM2 protein content in the spinal cord [28] whereas opioid antagonist decreases DNM2 abundance [29]. These changes in the level of DNM2 expression are inversely correlated with opioid receptor density at the plasma membrane, suggestive of feed-back regulation.

DNM2 function

Endocytosis DNM2 has been implicated in the formation of clathrin-coated pits (Fig. 2) [17]. In the cytosol, DNM2 forms a complex with sorting nexin 9 (SNX9) and fructose-1,6-bisphosphate aldolase [30]. Phosphorylation of SNX9 releases aldolase from the SNX9–DNM2 complex which is now competent for membrane targeting [30, 31]. DNM2 anchorage to the membrane occurs via interaction with PI4,5P2 membrane phosphoinositide [32] and BAR domain proteins, amphiphysin 1, amphiphysin 2, and SNX9 (Table 1) in curved sites of the membranes. DNM2 forms an oligomer helical structure around the neck of the nascent vesicles [17], and GTP hydrolysis is associated with the release of the vesicles. Interestingly, DNM2 co-localizes with clathrin before and during the internalization of the coated vesicle [6] suggesting that DNM2 plays also a role during the maturation of clathrin-coated pits [33].

DNM2 is also involved in clathrin-independent endocytosis by its participation in the formation of the phagosomes and caveolae [34, 35]. Predescu et al. described a protein complex, including DNM2, intersectin, and SNAP-23 that was important for the internalization of caveolae [36]. In caveolae, DNM2 also interacts with endothelial nitric-oxide synthase (eNOS) in bovine aortic endothelial cells [37] where DNM2 may regulate eNOS activation and the NO signaling cascade [37, 38]. DNM2 also participates in coat-independent endocytosis processes, i.e., micropinocytosis and macropinocytosis, by which fluid droplets and specific membrane components are internalized [39, 40].

Table 1 Direct or indirect interactions with DNM2

Name	OMIM	Site of interaction in DNM2	Function	Reference
Abp1	610106	nd	Endocytosis-actin bridge	[52, 95]
Amphiphysin 1	600418	PRD	Membrane trafficking	[14, 96]
Amphiphysin 2	601248	PRD	Membrane trafficking	[14, 97]
Annexin VI	114070	nd	Membrane trafficking	[98]
Aquaporin 2	107777	nd	Aquaporin trafficking	[99]
Arc	612461	PH	AMPA receptor trafficking	[100]
CAP	605264	nd	Actin remodeling during endocytosis	[101]
β-catenin	116806	nd	Blood–testis barrier integrity	[102]
Caveolin-1	601047	nd	Endocytosis	[73, 103, 104]
CBL	165360	nd	Actin remodeling during endocytosis	[105]
CIP4	604504	nd	GLUT4 trafficking	[106]
Complexin I	605032	nd	Acrosome formation and/or exocytosis	[107]
Complexin II	605033	nd	Acrosome formation and/or exocytosis	[107]
cortactin	164765	PRD	Actin assembly–endocytosis	[53, 54, 104]
c-Src	124095	PRD	Cell signaling and membrane trafficking	[108]
eNOS	163729	nd	NO production–cell signaling	[37, 109]
Ese1	602191	PRD	Endocytosis	[110]
FAK	600758	PRD	Focal adhesion disassembly	[58]
FBP17	606191	PRD	Actin reorganization during endocytosis	[111, 112]
Grb2	108355	PRD	Receptor internalization and signaling	[108, 113, 114]
IL-5Rα	147851	nd	IL-5 signaling pathway and trafficking	[115]
Jak2	147796	nd	IL-5 signaling pathway	[115]
JAM-A	605721	nd	Blood–testis barrier integrity	[102]
Kalirin 12	604605	GTPase	Membrane trafficking	[116]
KDR	191306	nd	Receptor signaling and expression	[117]
LYN	165120	PRD	IL-5 signaling pathway	[108, 115]
MLK2	600137	PRD	Actin (filipodia and membrane ruffles)	[118]
Myosin 1E	601479	PRD	Receptor-mediated endocytosis	[119]
N-cadherin	114020	nd	Blood–testis barrier integrity	[102]
Nef	–	MD / GED	HIV-1 entry	[120]
Nostrin	607496	PRD	eNOS trafficking	[121]
N-WASp	605056	nd	Actin remodeling	[56]
Occludin	602876	nd	Blood–testis barrier integrity	[102]
p85	171833	PRD		[108]
PDEγ	180073	nd	Cell signaling	[122]
PLCγ	172420	PRD		[108]
PLD2	602384	nd	Cell signaling	[123]
Shank 1	604999	PRD	Postsynaptic membrane turnover	[124]
Pyk2	601212	nd	Podosome dynamics	[125]
Shank 2	603290	PRD	Postsynaptic membrane turnover	[124]
SNX9	605952	PRD	Membrane remodeling–actin dynamics	[126, 127]
SNX18	–	PRD	Endosomal trafficking	[127]
SNX30	–	PRD	Membrane trafficking?	[127]
Syndapin 2	604960	PRD	Vesicle formation from the TGN	[45]
Syndecan-4	600017	PH	Actin-stress fibers and focal adhesion sites	[62]
Tks5/FISH	–	PRD	Cell signaling	[128]
TULA	605736	nd	EGFR trafficking	[129]
Vav1	164875	PRD	T cell activation by actin remodeling	[130]
β-tubulin	191130	PRD		[14]

Table 1 (continued)

Name	OMIM	Site of interaction in DNM2	Function	Reference
γ-adaptin	603533	PRD		[14]
γ-tubulin	191135	MD	Centrosome cohesion	[65]
ZO1	601009	nd	Blood–testis barrier integrity	[102]

Abp1 actin-binding protein, *CAP* CBL-associated protein, *CBL* Cas–Br–M murine ecotropic retroviral transforming sequence homolog, *CIP4* cdc42 interacting protein-4, *eNOS* endothelial nitric-oxide synthase, *Ese1* EH domain and SH3 regulator of endocytosis 1, *FAK* focal adhesion kinase, *FBP17* formin-binding protein 17, *Grb2* growth factor receptor-bound protein 2, *IL-5Rα* α subunit of the interleukin 5 receptor, *Jak2* Janus kinase 2, *JAM-A* junctional adhesion molecule A, *KDR* kinase insert domain receptor also known as: vascular endothelial growth factor receptor-2, *MLK2* mixed-lineage kinase 2, *Nef* accessory protein of the HIV-1, *N-WASp* Wiskott Aldrich syndrome protein, *PDEγ* inhibitory γ subunits of the retinal cGMP phosphodiesterase, *PLCγ* phospholipase C gamma 1, *PLD2* phospholipase D2, *SNX9* sorting nexin 9, *Tks5*/*FISH* tyrosine kinase substrate 5/five SH3 domains, *TULA* Cbl- and ubiquitin-interacting protein T-cell ubiquitin ligand, *Vav1* Rho family guanine nucleotide exchange factor Vav1, *ZO1* Zonula occludens 1

Intracellular membrane trafficking DNM2 is targeted to the Golgi apparatus where it is predominantly localized in the trans-Golgi network (TGN) [41]. Anti-DNM2 antibody injection and over-expression of DNM2 mutants impair vesicle formation from the TGN [42, 43]. Association of DNM2 with cortactin and syndapin 2 is required for trafficking of nascent vesicles from the TGN [44, 45]. DNM2 is also found at the clathrin-coated buds of early endosomes [46] and in late endosomes in Hela cells, located to the tubulo-vesicular appendices [47]. In these two cases, interfering DNM2 mutant impairs the recycling of components from the endosomal system towards the plasma membrane or TGN [46, 47]. These data highlight the role of DNM2 in the secretory pathway and in the sorting of cell components from the Golgi apparatus and endosomal compartment.

Exocytosis DNM2 may participate in endocytosis–exocytosis coupling as suggested in mouse pancreatic β-cells [48]. However, a role for DNM2 in exocytosis alone has been reported. During cell-mediated killing by natural killer (NK) cells, DNM2 co-localizes with lytic granules after NK cell activation and is required for fusion of the granules with the plasma membrane [49]. Similarly in macrophages, focal exocytosis is blocked after anti-DNM2 antibody microinjection [50], and DNM2 GTPase activity regulates the fusion of secretory vesicles at the plasma membrane [51]. Further studies will be necessary to precisely identify the molecular role played by DNM2 in the exocytosis machinery.

Actin network Actin-based dynamic processes are crucial for late-stage endocytosis and vesicle formation, and DNM2 interacts with the actin-binding proteins Abp1 (actin-binding protein 1) [52] and cortactin [53, 54]. Abp1 is an Src kinase which provides a physical bridge between the endocytosis machinery and the cortical actin network, and cortactin is a component of the clathrin-mediated

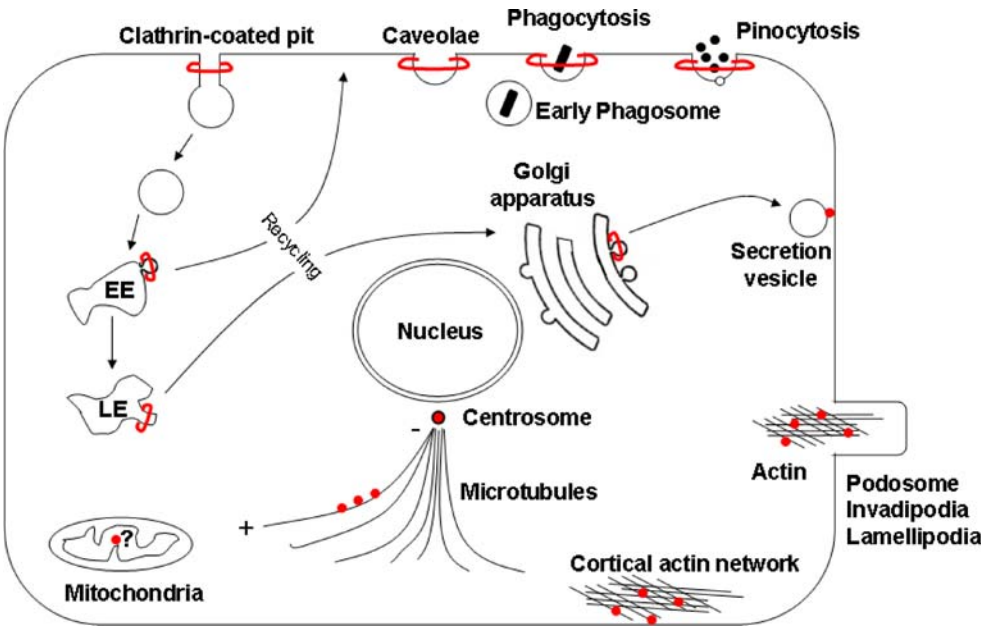

Fig. 2 DNM2 cellular functions. Representation of the multiple cellular localizations reported for DNM2 (*in red*)*EE* early endosome, *LE* late endosome

endocytosis machinery. However, interaction between DNM2 and the actin cytoskeleton may have another cytoskeletal role such as in the formation of membrane tubules and protrusions. Furthermore, a recent study showed the crucial function played by the DNM2-cortactin complex in the global organization and remodeling of the actomyosin cytoskeleton [55]. In addition, DNM2 is present in cortical ruffles and lamellipodia, both important in cell migration [10, 53]. The supramolecular complex including DNM2, cortactin, and Arp2/3 mediates the reorganization of actin allowing lamellipodia formation at the leading edge of migrating cells [56]. Disruption of DNM2 functions by DNM2-K44A mutant or small interfering RNA (siRNA) inhibits the formation of lamellipodia [57]. Similarly, under PDGF stimulation, DNM2 is concentrated within the leading ruffles of migrating fibroblasts where it co-localizes with cortactin [53]. To allow cell migration, DNM2 participates in disassembly of focal adhesions, as well as β-integrin internalization at the rear of the cell [58, 59]. Additionally, DNM2 is enriched in specialized membrane protrusions such as podosomes and invadipodia. Podosomes represent attachment sites between cells and substratum [60], and invadipodia are focalized matrix degradation sites [61]. Inhibition of DNM2 diminishes the amount of such structures [61]. It has also been shown that DNM2 regulates the formation of actin-stress fibers by interaction with the cell surface heparin sulfate proteoglycan syndecan-4 [62]. Expression of DNM2-mutant, truncated for the PRD domain mediating interaction with cortactin, increases the number of actin-stress fibers, which is associated with abnormal cell shape [53].

Microtubule network and MTOC DNM2 interacts with microtubules [17, 63], and the binding region was located to the PRD [5, 64]. It was shown that down-regulation of DNM2 by siRNA increases the amount of acetylated tubulin, a more stable form of tubulin in microtubules and reduces their growing capacity [63], suggesting that DNM2 may regulate the polymerization–depolymerization equilibrium of microtubules. Through its interaction with microtubules, DNM2 appears involved in Golgi apparatus cohesion [63]. Moreover, DNM2 has been identified as a component of the centrosome, the main microtubule organizing center (MTOC), where it binds to γ-tubulin [65]. The centrosome consists of a pair of centrioles embedded in a filamentous pericentriolar matrix, where γ-tubulin is essential for microtubule nucleation. The function played by DNM2 at the centrosome is still unknown, but DNM2 silencing by siRNA suggests a role in centrosome splitting [65]. Likewise, participation of DNM2 in all the phases of mitosis has also been reported. DNM2 is detected in the two MTOC during early prophase, along the mitotic spindle during metaphase and in the spindle midzone region during anaphase and early telophase [66]. Thereafter, DNM2 is accumulated at the intracellular bridge where the final separation occurs. The time required for separation of the two daughter cells is longer in DNM2 knock-out cells [40]. Taken together, these data suggest that DNM2 may regulate microtubule-dependent processes by acting on microtubule dynamics and organization.

Apoptosis In order to establish a stable Hela cell line over-expressing DNM2 isoform 2, Fish et al. have reported a significant cell toxicity in dividing cells [67]. The cytotoxicity occurred via induction of apoptosis by a p53-dependent mechanism. Similar results were gained in vascular smooth muscle cells [68]. The capacity to trigger apoptosis appears DNM2-specific as DNM1 over-expression does not induce apoptosis [67]. The GTPase domain of DNM2 is crucial to induce apoptosis [69]. In addition, a point mutation (p. I684K) in the DNM2 GED enhances the apoptosis induction by the wild-type DNM2 suggesting that GED negatively regulates this DNM2 function [69]. Mitochondria are key players in apoptosis and, interestingly, DNM2 has been detected in isolated mitochondria from bovine lymphoblastoid BL-3 cells [70]. However, to our knowledge, such localization has not been reported in other cell lines or tissues. DNM2 also regulates the apoptosis-inducing Fas–Fas ligand pathway by facilitating the transport of Fas from the trans-Golgi network to the plasma membrane [71].

Specific functions of DNM2 isoforms In a cultured rat epithelial cell line (clone 9), both DNM2 isoforms 1 and 3 show punctuate labeling of clathrin heavy chain-positive or heavy chain-negative structures, but only isoform 1, with the GEIL sequence in the MD, appears located to the Golgi apparatus [10]. These data suggest a role for the GEIL sequence in targeting to the Golgi apparatus. However, cell-type specificity probably exists, as isoforms without the GEIL sequence were also shown to be targeted to the Golgi apparatus in MDCK cells [43], 3T3L1 adipocytes [72], and fibroblastoid-like cells derived from mouse embryonic stem cells [40]. Nevertheless, this possible differential localization argues for distinct functions. Indeed, in clone 9 cells, the K44A mutants of isoforms 2 and 4 are able to inhibit fluid-phase endocytosis, whereas the mutant forms of isoforms 1 and 3 do not [39] and are also more potent inhibitors of clathrin-mediated endocytosis. Similarly, in a hepatocyte cell line, the K44A-isoform 1 inhibits caveolae-dependent internalization, but not the other K44A mutant isoforms [73]. In fibroblastoid-like cells derived from mouse embryonic stem cells, isoforms 2 and 4 are the most efficient at rescuing export from the Golgi in DNM2 knock-out cells [40]. Altogether, these data suggest a preferential involvement of isoforms 1 and 3 in clathrin- and caveolae-dependent endocytosis, whereas isoforms 2

and 4 participate in uncoated endocytosis and trafficking from the Golgi apparatus. However, cell-type specificity also occurs as the four isoforms exhibit a similar subcellular distribution in 3T3L1 adipocytes, and dominant negative mutants of each isoform similarly affect basal and insulin-stimulated GLUT4 trafficking [72].

DNM2 and human diseases

Mutations in the *DNM2* gene cause rare forms of the Charcot–Marie-Tooth peripheral neuropathy (CMT) [2, 74–77] and autosomal dominant centronuclear myopathy (CNM) [3, 11, 78–80]. The 19 reported heterozygous mutations affect only the MD, the PH domain, and the GED (Fig. 1b). DNM2-related CNM is a slowly progressive congenital myopathy characterized by frequent centrally located nuclei in muscle fibers. The most common clinical features are delayed motor milestones, facial and generalized muscle weakness, ptosis, and ophthalmoplegia [81]. Nevertheless, the severity of DNM2-CNM is variable, ranging from severe neonatal to mild late-onset forms. DNM2-CMT is a peripheral neuropathy characterized by progressive muscle weakness and atrophy. *DNM2* mutations can cause axonal CMT (CMT2) and dominant intermediate CMT (DI-CMT-B). In some CMT patients, neuropathy is associated with neutropenia [2, 75, 77] but this association has not been described in DNM2-CNM patients. Clinical overlap could exist in some patients [81], but the majority of patients are affected by a tissue-specific disorder. No clear genotype–phenotype relationship can be generated, except for the de novo mutations located in the C-terminal part of the PH domain, which are all associated with a severe neonatal CNM phenotype [98]. In these patients, the phenotype progressively improves, suggesting compensatory mechanisms.

More recently, the *DNM2* gene has been described as a susceptibility gene for late-onset Alzheimer disease [82], and DNM2 expression was found to be decreased in the brains of these patients [83]. Cognitive impairments have been reported in some CNM patients harboring the p.E368Q [78], p.R465W [84; Family 1], and p.R369Q [84; Families 2 and 3] DNM2 mutations. Future studies will be necessary to determine the prevalence of central nervous system involvement in DNM2-related diseases.

Pathophysiological hypotheses

The DNM2 mutations identified so far in CNM and CMT are heterozygous missense mutations or small deletions (Fig. 1). We have shown that DNM2 transcript, protein expression, and localization are normal in fibroblasts from CNM patients [3, 11]. These data are in agreement with DNM2 mutants having a dominant negative effect, resulting in a loss of function of DNM2 in endocytosis [11] or in microtubule-related functions [63] (see below).

Membrane trafficking and signaling pathway hypothesis In addition to the *DNM2* mutations in autosomal dominant CNM, mutations in the *BIN1* gene encoding amphiphysin 2, a partner of DNM2 in the endocytic process, cause the autosomal recessive form of the disease [85]. This suggests that endocytic impairment is a potential pathomechanism of autosomal CNM. Indeed, impairment of clathrin-mediated endocytosis was reported in cultured cells expressing CNM- or CMT-DNM2 mutants [2, 11, 63]. Among these studies, one CMT-mutant was unable to block the uptake of transferrin, a marker of clathrin-mediated receptor endocytosis [63]. Nevertheless, the transferrin-containing compartment was not located to the perinuclear region after 30 min of incubation showing that its intracellular trafficking was impaired by the CMT-mutant. The crucial question which remains to be explored is how a defect in endocytosis can alter the cell function, especially in a tissue-specific manner. On one hand, inhibition of DNM2-dependent trafficking may lead to a decrease in receptor stimulated signaling as shown for the MAPK ERK1/2 pathway [11]. On the other hand, DNM2 mutations may lead to a prolonged half-life of various proteins at the cell surface due to a defect in protein removal, as shown for the GLUT4 glucose transporter [72]. A deregulation of glucose transport in patients with DNM2 mutations could have a strong impact on muscle fibers given their high glucose consumption.

To date, the impact of disease-associated DNM2 mutants on other DNM2-dependent membrane trafficking processes, especially in endosomal and Golgi pathways, has not been studied. We cannot exclude a participation of these pathways in the pathomechanisms of DNM2-related disorders.

Cytoskeleton impairment and its putative role on nuclear positioning In DNM2-CNM, the majority of patients harbor a mutation in the MD, which is essential for the centrosomal localization of DNM2 and for its interaction with γ-tubulin [65]. Previous results in skin fibroblasts indicate that transfected GFP-DNM2-mutants fail to correctly target to the centrosome, suggesting that DNM2 mutations might cause CNM by interfering with centrosomal functions [3]. In addition, CMT-related DNM2 mutants can disorganize the microtubule cytoskeleton [2], and one particular CMT-mutant was shown to impair microtubule-dependent membrane transport [63]. In addition to their roles in intracellular trafficking, the microtubule and actin networks regulate cellular architecture including nuclear positioning [86, 87]. Thus, cytoskeletal impairment may

play a role in the abnormal central location of the nuclei in the muscle fibers in CNM. In CMT, DNM2 mutations could also induce a destabilization of the microtubule network leading to abnormal axonal transport and protein trafficking, a pathophysiological mechanism described previously in various forms of CMT [88].

T-tubule hypothesis in CNM The X-linked recessive form of CNM (also called XLMTM for X-linked myotubular myopathy) is due to mutations in the *MTM1* gene encoding the myotubularin, and the autosomal recessive and dominant CNMs result from mutations of amphiphysin 2 and DNM2, respectively [89]. The muscle specific isoform of amphiphysin 2 is concentrated at T-tubules in mouse and drosophila and is involved in the organization of this plasma membrane invagination acting in excitation–contraction coupling [90, 91]. Myotubularin is also located to the T-tubules in mouse [92] and zebrafish [93], and knock-down of myotubularin in these species leads to disorganization of the T-tubule system, reduction in Ca^{2+} release from the sarcoplasmic reticulum, and defect in excitation–contraction coupling [93, 94]. In addition, abnormal localization of T-tubule markers was shown in muscle biopsies from *BIN1*-CNM and *MTM1*-CNM patients [85, 93], suggesting that an excitation–contraction coupling impairment due to T-tubule dysfunction could be a common pathomechanism leading to muscle weakness in CNMs. Future studies are necessary to explore this hypothesis in the *DNM2*-CNM in which no morphological abnormalities of the T-tubule system have been reported to date.

Concluding remarks and open questions

Given the numerous distinct functions in which the ubiquitously expressed DNM2 is involved, the identification of pathophysiological mechanisms will be a challenge. The phenotypes encountered in CNM and CMT patients could be due to impairment of the various functions of the protein. To date, there is no explanation for the tissue-specific impact of the DNM2-mutations in human diseases. DNM2 is engaged in numerous protein–protein interactions (Table 1), but these interactions in muscles and nerves are largely unexplored. Another unresolved question is whether each particular mutation can similarly affect the functions of the four DNM2 isoforms. Finally, whereas some data emerge on the impact of disease-related DNM2 mutations on the microtubule network, their impact on the actin cytoskeleton is totally unknown. Future developments of animal models will certainly be useful to better determine the main functions of DNM2 in vivo, especially in skeletal muscle and nerves where membrane trafficking displays unique cell length dependent characteristics.

Acknowledgements We thank Dr. Rachel Peat and Dr. Edgar Gomes for helpful advice. Anne-Cécile Durieux was the recipient of a fellowship from the Association Française contre les Myopathies (AFM).

References

1. Heymann JA, Hinshaw JE (2009) Dynamins at a glance. J Cell Sci 122:3427–3431
2. Zuchner S, Noureddine M, Kennerson M, Verhoeven K, Claeys K, De Jonghe P, Merory J, Oliveira SA, Speer MC, Stenger JE, Walizada G, Zhu D, Pericak-Vance MA, Nicholson G, Timmerman V, Vance JM (2005) Mutations in the pleckstrin homology domain of dynamin 2 cause dominant intermediate Charcot–Marie-Tooth disease. Nat Genet 37:289–294
3. Bitoun M, Maugenre S, Jeannet PY, Lacène E, Ferrer X, Laforêt P, Martin JJ, Laporte J, Lochmuller H, Beggs AH, Fardeau M, Eymard B, Romero NB, Guicheney P (2005) Mutations in dynamin 2 cause dominant centronuclear myopathy. Nature Genet 37:1207–1209
4. Sontag JM, Fykse EM, Ushkaryov Y, Liu JP, Robinson PJ, Sudhof TC (1994) Differential expression and regulation of multiple dynamins. J Biol Chem 269:4547–4554
5. Lin HC, Barylko B, Achiriloaie M, Albanesi JP (1997) Phosphatidylinositol (4, 5)-bisphosphate-dependent activation of dynamins I and II lacking the proline/arginine-rich domains. J Biol Chem 272:25999–26004
6. Rappoport JZ, Simon SM (2003) Real-time analysis of clathrin-mediated endocytosis during cell migration. J Cell Sci 116:847–855
7. Artalejo CR, Elhamdani A, Palfrey HC (2002) Sustained stimulation shifts the mechanism of endocytosis from dynamin-1-dependent rapid endocytosis to clathrin- and dynamin-2-mediated slow endocytosis in chromaffin cells. Proc Natl Acad Sci USA 99:6358–6363
8. Cook TA, Urrutia R, McNiven MA (1994) Identification of dynamin 2, an isoform ubiquitously expressed in rat tissues. Proc Natl Acad Sci USA 91:644–648
9. Diatloff-Zito C, Gordon AJ, Duchaud E, Merlin G (1995) Isolation of an ubiquitously expressed cDNA encoding human dynamin II, a member of the large GTP-binding protein family. Gene 163:301–306
10. Cao H, Garcia F, McNiven MA (1998) Differential distribution of dynamin isoforms in mammalian cells. Mol Biol Cell 9:2595–2609
11. Bitoun M, Durieux AC, Prudhon B, Bevilacqua JA, Herledan A, Sakanyan V, Urtizberea A, Cartier L, Romero NB, Guicheney P (2009) Dynamin 2 mutations associated with human diseases impair clathrin-mediated receptor endocytosis. Hum Mutat 30:1419–1427
12. Smirnova E, Shurland DL, Newman-Smith ED, Pishvaee B, van der Bliek AM (1999) A model for dynamin self-assembly based on binding between three different protein domains. J Biol Chem 274:14942–14947
13. Chen YJ, Zhang P, Egelman EH, Hinshaw JE (2004) The stalk region of dynamin drives the constriction of dynamin tubes. Nat Struct Mol Biol 11:574–575
14. Dong J, Misselwitz R, Welfle H, Westermann P (2000) Expression and purification of dynamin II domains and initial studies on structure and function. Protein Expr Purif 20:314–323
15. Klein DE, Lee A, Frank DW, Marks MS, Lemmon MA (1998) The pleckstrin homology domains of dynamin isoforms require

oligomerization for high affinity phosphoinositide binding. J Biol Chem 273:27725–27733
16. Sever S, Muhlberg AB, Schmid SL (1999) Impairment of dynamin's GAP domain stimulates receptor-mediated endocytosis. Nature 398:481–486
17. Warnock DE, Baba T, Schmid SL (1997) Ubiquitously expressed dynamin-II has a higher intrinsic GTPase activity and a greater propensity for self-assembly than neuronal dynamin-I. Mol Biol Cell 8:2553–2562
18. Eccleston JF, Binns DD, Davis CT, Albanesi JP, Jameson DM (2002) Oligomerization and kinetic mechanism of the dynamin GTPase. Eur Biophys J 31:275–282
19. Soulet F, Yarar D, Leonard M, Schmid SL (2005) SNX9 regulates dynamin assembly and is required for efficient clathrin-mediated endocytosis. Mol Biol Cell 16:2058–2067
20. Solomaha E, Palfrey HC (2005) Conformational changes in dynamin on GTP binding and oligomerization reported by intrinsic and extrinsic fluorescence. Biochem J 391:601–611
21. Shajahan AN, Timblin BK, Sandoval R, Tiruppathi C, Malik AB, Minshall RD (2004) Role of Src-induced dynamin-2 phosphorylation in caveolae-mediated endocytosis in endothelial cells. J Biol Chem 279:20392–20400
22. Efendiev R, Yudowski GA, Zwiller J, Leibiger B, Katz AI, Berggren PO, Pedemonte CH, Leibiger IB, Bertorello AM (2002) Relevance of dopamine signals anchoring dynamin-2 to the plasma membrane during Na+, K+-ATPase endocytosis. J Biol Chem 277:44108–44114
23. Kang-Decker N, Cao S, Chatterjee S, Yao J, Egan LJ, Semela D, Mukhopadhyay D, Shah V (2007) Nitric oxide promotes endothelial cell survival signaling through S-nitrosylation and activation of dynamin-2. J Cell Sci 120:492–501
24. Sever S, Altintas MM, Nankoe SR, Moller CC, Ko D, Wei C, Henderson J, del Re EC, Hsing L, Erickson A, Cohen CD, Kretzler M, Kerjaschki D, Rudensky A, Nikolic B, Reiser J (2007) Proteolytic processing of dynamin by cytoplasmic cathepsin L is a mechanism for proteinuric kidney disease. J Clin Invest 117:2095–2104
25. Cousin MA, Robinson PJ (2000) Ca(2+) influx inhibits dynamin and arrests synaptic vesicle endocytosis at the active zone. J Neurosci 20:949–957
26. Cook TA, Mesa KJ, Gebelein BA, Urrutia RA (1996) Upregulation of dynamin II expression during the acquisition of a mature pancreatic acinar cell phenotype. J Histochem Cytochem 44:1373–1378
27. Cook T, Mesa K, Urrutia R (1996) Three dynamin-encoding genes are differentially expressed in developing rat brain. J Neurochem 67:927–931
28. Zhang Q, Purohit V, Yoburn BC (2005) Continuous opioid agonist treatment dose-dependently regulates mu-opioid receptors and dynamin-2 in mouse spinal cord. Synapse 56:123–128
29. Rajashekara V, Patel CN, Patel K, Purohit V, Yoburn BC (2003) Chronic opioid antagonist treatment dose-dependently regulates mu-opioid receptors and trafficking proteins in vivo. Pharmacol Biochem Behav 75:909–913
30. Lundmark R, Carlsson SR (2004) Regulated membrane recruitment of dynamin-2 mediated by sorting nexin 9. J Biol Chem 279:42694–42702
31. Lundmark R, Carlsson SR (2005) Expression and properties of sorting nexin 9 in dynamin-mediated endocytosis. Methods Enzymol 404:545–556
32. Zoncu R, Perera RM, Sebastian R, Nakatsu F, Chen H, Balla T, Ayala G, Toomre D, De Camilli PV (2007) Loss of endocytic clathrin-coated pits upon acute depletion of phosphatidylinositol 4, 5-bisphosphate. Proc Natl Acad Sci USA 104:3793–3798
33. Loerke D, Mettlen M, Yarar D, Jaqaman K, Jaqaman H, Danuser G, Schmid SL (2009) Cargo and dynamin regulate clathrin-coated pit maturation. PLoS Biol 7:e57
34. Gold ES, Underhill DM, Morrissette NS, Guo J, McNiven MA, Aderem A (1999) Dynamin 2 is required for phagocytosis in macrophages. J Exp Med 190:1849–1856
35. Henley JR, Krueger EW, Oswald BJ, McNiven MA (1998) Dynamin-mediated internalization of caveolae. J Cell Biol 141:85–99
36. Predescu SA, Predescu DN, Timblin BK, Stan RV, Malik AB (2003) Intersectin regulates fission and internalization of caveolae in endothelial cells. Mol Biol Cell 14:4997–5010
37. Cao S, Yao J, McCabe TJ, Yao Q, Katusic ZS, Sessa WC, Shah V (2001) Direct interaction between endothelial nitric-oxide synthase and dynamin-2. Implications for nitric-oxide synthase function. J Biol Chem 276:14249–14256
38. Sanchez FA, Rana R, Kim DD, Iwahashi T, Zheng R, Lal BK, Gordon DM, Meininger CJ, Duran WN (2009) Internalization of eNOS and NO delivery to subcellular targets determine agonist-induced hyperpermeability. Proc Natl Acad Sci USA 106:6849–6853
39. Cao H, Chen J, Awoniyi M, Henley JR, McNiven MA (2007) Dynamin 2 mediates fluid-phase micropinocytosis in epithelial cells. J Cell Sci 120:4167–4177
40. Liu YW, Surka MC, Schroeter T, Lukiyanchuk V, Schmid SL (2008) Isoform and splice-variant specific functions of dynamin-2 revealed by analysis of conditional knock-out cells. Mol Biol Cell 19:5347–5359
41. Maier O, Knoblich M, Westermann P (1996) Dynamin II binds to the trans-Golgi network. Biochem Biophys Res Commun 223:229–233
42. Jones SM, Howell KE, Henley JR, Cao H, McNiven MA (1998) Role of dynamin in the formation of transport vesicles from the trans-Golgi network. Science 279:573–577
43. Kreitzer G, Marmorstein A, Okamoto P, Vallee R, Rodriguez-Boulan E (2000) Kinesin and dynamin are required for post-Golgi transport of a plasma-membrane protein. Nat Cell Biol 2:125–127
44. Cao H, Weller S, Orth JD, Chen J, Huang B, Chen JL, Stamnes M, McNiven MA (2005) Actin and Arf1-dependent recruitment of a cortactin–dynamin complex to the Golgi regulates post-Golgi transport. Nat Cell Biol 7:483–492
45. Kessels MM, Dong J, Leibig W, Westermann P, Qualmann B (2006) Complexes of syndapin II with dynamin II promote vesicle formation at the trans-Golgi network. J Cell Sci 119:1504–1516
46. van Dam EM, Stoorvogel W (2002) Dynamin-dependent transferrin receptor recycling by endosome-derived clathrin-coated vesicles. Mol Biol Cell 13:169–182
47. Nicoziani P, Vilhardt F, Llorente A, Hilout L, Courtoy PJ, Sandvig K, van Deurs B (2000) Role for dynamin in late endosome dynamics and trafficking of the cation-independent mannose 6-phosphate receptor. Mol Biol Cell 11:481–495
48. Min L, Leung YM, Tomas A, Watson RT, Gaisano HY, Halban PA, Pessin JE, Hou JC (2007) Dynamin is functionally coupled to insulin granule exocytosis. J Biol Chem 282:33530–33536
49. Arneson LN, Segovis CM, Gomez TS, Schoon RA, Dick CJ, Lou Z, Billadeau DD, Leibson PJ (2008) Dynamin 2 regulates granule exocytosis during NK cell-mediated cytotoxicity. J Immunol 181:6995–7001
50. Di A, Nelson DJ, Bindokas V, Brown ME, Libunao F, Palfrey HC (2003) Dynamin regulates focal exocytosis in phagocytosing macrophages. Mol Biol Cell 14:2016–2028
51. Jaiswal JK, Rivera VM, Simon SM (2009) Exocytosis of post-Golgi vesicles is regulated by components of the endocytic machinery. Cell 137:1308–1319
52. Kessels MM, Engqvist-Goldstein AE, Drubin DG, Qualmann B (2001) Mammalian Abp1, a signal-responsive F-actin-binding protein, links the actin cytoskeleton to endocytosis via the GTPase dynamin. J Cell Biol 153:351–366

53. McNiven MA, Kim L, Krueger EW, Orth JD, Cao H, Wong TW (2000) Regulated interactions between dynamin and the actin-binding protein cortactin modulate cell shape. J Cell Biol 151:187–198
54. Schafer DA, Weed SA, Binns D, Karginov AV, Parsons JT, Cooper JA (2002) Dynamin2 and cortactin regulate actin assembly and filament organization. Curr Biol 12:1852–1857
55. Mooren OL, Kotova TI, Moore AJ, Schafer DA (2009) Dynamin2 GTPase and cortactin remodel actin filaments. J Biol Chem 284:23995–24005
56. Krueger EW, Orth JD, Cao H, McNiven MA (2003) A dynamin-cortactin-Arp2/3 complex mediates actin reorganization in growth factor-stimulated cells. Mol Biol Cell 14:1085–1096
57. Schlunck G, Damke H, Kiosses WB, Rusk N, Symons MH, Waterman-Storer CM, Schmid SL, Schwartz MA (2004) Modulation of Rac localization and function by dynamin. Mol Biol Cell 15:256–267
58. Ezratty EJ, Partridge MA, Gundersen GG (2005) Microtubule-induced focal adhesion disassembly is mediated by dynamin and focal adhesion kinase. Nat Cell Biol 7:581–590
59. Vassilieva EV, Gerner-Smidt K, Ivanov AI, Nusrat A (2008) Lipid rafts mediate internalization of beta1-integrin in migrating intestinal epithelial cells. Am J Physiol Gastrointest Liver Physiol 295:G965–G976
60. Ochoa GC, Slepnev VI, Neff L, Ringstad N, Takei K, Daniell L, Kim W, Cao H, McNiven M, Baron et a (2000) A functional link between dynamin and the actin cytoskeleton at podosomes. J Cell Biol 150:377–389
61. Baldassarre M, Pompeo A, Beznoussenko G, Castaldi C, Cortellino S, McNiven MA, Luini A, Buccione R (2003) Dynamin participates in focal extracellular matrix degradation by invasive cells. Mol Biol Cell 14:1074–1084
62. Yoo J, Jeong MJ, Cho HJ, Oh ES, Han MY (2005) Dynamin II interacts with syndecan-4, a regulator of focal adhesion and stress-fiber formation. Biochem Biophys Res Commun 328:424–431
63. Tanabe K, Takei K (2009) Dynamic instability of microtubules requires dynamin 2 and is impaired in a Charcot–Marie-Tooth mutant. J Cell Biol 185:939–948
64. Hamao K, Morita M, Hosoya H (2009) New function of the proline rich domain in dynamin-2 to negatively regulate its interaction with microtubules in mammalian cells. Exp Cell Res 315:1336–1345
65. Thompson HM, Cao H, Chen J, Euteneuer U, McNiven MA (2004) Dynamin 2 binds gamma-tubulin and participates in centrosome cohesion. Nat Cell Biol 6:335–342
66. Thompson HM, Skop AR, Euteneuer U, Meyer BJ, McNiven MA (2002) The large GTPase dynamin associates with the spindle midzone and is required for cytokinesis. Curr Biol 12:2111–2117
67. Fish KN, Schmid SL, Damke H (2000) Evidence that dynamin-2 functions as a signal-transducing GTPase. J Cell Biol 150:145–154
68. Kashiwakura Y, Watanabe M, Kusumi N, Sumiyoshi K, Nasu Y, Yamada H, Sawamura T, Kumon H, Takei K, Daida H (2004) Dynamin-2 regulates oxidized low-density lipoprotein-induced apoptosis of vascular smooth muscle cell. Circulation 110:3329–3334
69. Soulet F, Schmid SL, Damke H (2006) Domain requirements for an endocytosis-independent, isoform-specific function of dynamin-2. Exp Cell Res 312:3539–3545
70. Atapattu DN, Albrecht RM, McClenahan DJ, Czuprynski CJ (2008) Dynamin-2-dependent targeting of Mannheimia haemolytica leukotoxin to mitochondrial cyclophilin D in bovine lymphoblastoid cells. Infect Immun 76:5357–5365
71. Ivanov VN, Ronai Z, Hei TK (2006) Opposite roles of FAP-1 and dynamin in the regulation of Fas (CD95) translocation to the cell surface and susceptibility to Fas ligand-mediated apoptosis. J Biol Chem 281:1840–1852
72. Kao AW, Yang C, Pessin JE (2000) Functional comparison of the role of dynamin 2 splice variants on GLUT-4 endocytosis in 3T3L1 adipocytes. Am J Physiol Endoc M 278:E825–E831
73. Yao Q, Chen J, Cao H, Orth JD, McCaffery JM, Stan RV, McNiven MA (2005) Caveolin-1 interacts directly with dynamin-2. J Mol Biol 348:491–501
74. Fabrizi GM, Ferrarini M, Cavallaro T, Cabrini I, Cerini R, Bertolasi L, Rizzuto N (2007) Two novel mutations in dynamin-2 cause axonal Charcot–Marie-Tooth disease. Neurology 69:291–295
75. Bitoun M, Stojkovic T, Prudhon B, Maurage CA, Latour P, Vermersch P, Guicheney P (2008) A novel mutation in the dynamin 2 gene in a Charcot–Marie-Tooth type 2 patient: clinical and pathological findings. Neuromuscul Disord 18:334–338
76. Gallardo E, Claeys KG, Nelis E, Garcia A, Canga A, Combarros O, Timmerman V, De Jonghe P, Berciano J (2008) Magnetic resonance imaging findings of leg musculature in Charcot–Marie-Tooth disease type 2 due to dynamin 2 mutation. J Neurol 255:986–992
77. Claeys KG, Zuchner S, Kennerson M, Berciano J, Garcia A, Verhoeven K, Storey E, Merory JR, Bienfait HM, Lammens M, Nelis E, Baets J, De Vriendt E, Berneman ZN, De Veuster I, Vance JM, Nicholson G, Timmerman V, De Jonghe P (2009) Phenotypic spectrum of dynamin 2 mutations in Charcot–Marie-Tooth neuropathy. Brain 132:1741–1752
78. Echaniz-Laguna A, Nicot AS, Carre S, Franques J, Tranchant C, Dondaine N, Biancalana V, Mandel JL, Laporte J (2007) Subtle central and peripheral nervous system abnormalities in a family with centronuclear myopathy and a novel dynamin 2 gene mutation. Neuromuscul Disord 17:955–959
79. Bitoun M, Bevilacqua JA, Prudhon B, Maugenre S, Taratuto AL, Monges S, Lubieniecki F, Cances C, Uro-Coste E, Mayer M, Fardeau M, Romero NB, Guicheney P (2007) Dynamin 2 mutations cause sporadic centronuclear myopathy with neonatal onset. Ann Neurol 62:666–670
80. Bitoun M, Bevilacqua JA, Eymard B, Prudhon B, Fardeau M, Guicheney P, Romero NB (2009) A new centronuclear myopathy phenotype due to a novel dynamin 2 mutation. Neurology 72:93–95
81. Fischer D, Herasse M, Bitoun M, Barragán-Campos HM, Chiras J, Laforêt P, Fardeau M, Eymard B, Guicheney P, Romero NB (2006) Characterization of the muscle involvement in dynamin 2- related centronuclear myopathy. Brain 129:1463–1469
82. Aidaralieva NJ, Kamino K, Kimura R, Yamamoto M, Morihara T, Kazui H, Hashimoto R, Tanaka T, Kudo T, Kida T, Okuda J, Uema T, Yamagata H, Miki T, Akatsu H, Kosaka K, Takeda M (2008) Dynamin 2 gene is a novel susceptibility gene for late-onset Alzheimer disease in non-APOE-epsilon4 carriers. J Hum Genet 53:296–302
83. Kamagata E, Kudo T, Kimura R, Tanimukai H, Morihara T, Sadik MG, Kamino K, Takeda M (2009) Decrease of dynamin 2 levels in late-onset Alzheimer's disease alters Abeta metabolism. Biochem Biophys Res Commun 379:691–695
84. Jeannet PY, Bassez G, Eymard B, Laforet P, Urtizberea JA, Rouche A, Guicheney P, Fardeau M, Romero NB (2004) Clinical and histologic findings in autosomal centronuclear myopathy. Neurology 62:1484–1490
85. Nicot AS, Toussaint A, Tosch V, Kretz C, Wallgren-Pettersson C, Iwarsson E, Kingston H, Garnier JM, Biancalana V, Oldfors A, Mandel JL, Laporte J (2007) Mutations in amphiphysin 2 (BIN1) disrupt interaction with dynamin 2 and cause autosomal recessive centronuclear myopathy. Nat Genet 39:1134–1139

86. Morris NR (2003) Nuclear positioning: the means is at the ends. Curr Opin Cell Biol 15:54–59
87. Starr DA, Han M (2003) ANChors away: an actin based mechanism of nuclear positioning. J Cell Sci 116:211–216
88. Shy ME (2004) Charcot–Marie-Tooth disease: an update. Curr Opin Neurol 17:579–585
89. Jungbluth H, Wallgren-Pettersson C, Laporte J (2008) Centronuclear (myotubular) myopathy. Orphanet J Rare Dis 3:26–38
90. Lee E, Marcucci M, Daniell L, Pypaert M, Weisz OA, Ochoa GC, Farsad K, Wenk MR, De Camilli P (2002) Amphiphysin 2 (Bin1) and T-tubule biogenesis in muscle. Science 297:1193–1196
91. Razzaq A, Robinson IM, McMahon HT, Skepper JN, Su Y, Zelhof AC, Jackson AP, Gay NJ, O'Kane CJ (2001) Amphiphysin is necessary for organization of the excitation-contraction coupling machinery of muscles, but not for synaptic vesicle endocytosis in drosophila. Genes Dev 15:2967–2979
92. Buj-Bello A, Fougerousse F, Schwab Y, Messaddeq N, Spehner D, Pierson CR, Durand M, Kretz C, Danos O, Douar AM, Beggs AH, Schultz P, Montus M, Denefle P, Mandel JL (2008) AAV-mediated intramuscular delivery of myotubularin corrects the myotubular myopathy phenotype in targeted murine muscle and suggests a function in plasma membrane homeostasis. Hum Mol Genet 17:2132–2143
93. Dowling JJ, Vreede AP, Low SE, Gibbs EM, Kuwada JY, Bonnemann CG, Feldman EL (2009) Loss of myotubularin function results in T-tubule disorganization in zebrafish and human myotubular myopathy. PLoS Genet 5:e1000372
94. Al-Qusairi L, Weiss N, Toussaint A, Berbey C, Messaddeq N, Kretz C, Sanoudou D, Beggs AH, Allard B, Mandel JL, Laporte J, Jacquemond V, Buj-Bello A (2009) T-tubule disorganization and defective excitation-contraction coupling in muscle fibers lacking myotubularin lipid phosphatase. Proc Natl Acad Sci USA 106:18763–18768
95. Onabajo OO, Seeley MK, Kale A, Qualmann B, Kessels M, Han J, Tan TH, Song W (2008) Actin-binding protein 1 regulates B cell receptor-mediated antigen processing and presentation in response to B cell receptor activation. J Immunol 180:6685–6695
96. Nakanishi A, Abe T, Watanabe M, Takei K, Yamada H (2008) Dynamin 2 cooperates with amphiphysin 1 in phagocytosis in sertoli cells. Acta Med Okayama 62:385–391
97. Kojima C, Hashimoto A, Yabuta I, Hirose M, Hashimoto S, Kanaho Y, Sumimoto H, Ikegami T, Sabe H (2004) Regulation of Bin1 SH3 domain binding by phosphoinositides. EMBO J 23:4413–4422
98. Turpin E, Russo-Marie F, Dubois T, de Paillerets C, Alfsen A, Bomsel M (1998) In adrenocortical tissue, annexins II and VI are attached to clathrin coated vesicles in a calcium-independent manner. Biochim Biophys Acta 1402:115–130
99. Lu HA, Sun TX, Matsuzaki T, Yi XH, Eswara J, Bouley R, McKee M, Brown D (2007) Heat shock protein 70 interacts with aquaporin-2 and regulates its trafficking. J Biol Chem 282:28721–28732
100. Chowdhury S, Shepherd JD, Okuno H, Lyford G, Petralia RS, Plath N, Kuhl D, Huganir RL, Worley PF (2006) Arc/Arg3.1 interacts with the endocytic machinery to regulate AMPA receptor trafficking. Neuron 52:445–459
101. Tosoni D, Cestra G (2009) CAP (Cbl associated protein) regulates receptor-mediated endocytosis. FEBS Lett 583:293–300
102. Lie PP, Xia W, Wang CQ, Mruk DD, Yan HH, Wong CH, Lee WM, Cheng CY (2006) Dynamin II interacts with the cadherin- and occludin-based protein complexes at the blood-testis barrier in adult rat testes. J Endocrinol 191:571–586
103. Kim YN, Bertics PJ (2002) The endocytosis-linked protein dynamin associates with caveolin-1 and is tyrosine phosphorylated in response to the activation of a noninternalizing epidermal growth factor receptor mutant. Endocrinology 143:1726–1731
104. Singleton PA, Salgia R, Moreno-Vinasco L, Moitra J, Sammani S, Mirzapoiazova T, Garcia JG (2007) CD44 regulates hepatocyte growth factor-mediated vascular integrity. Role of c-Met, Tiam1/Rac1, dynamin 2, and cortactin. J Biol Chem 282:30643–30657
105. Bruzzaniti A, Neff L, Sanjay A, Horne WC, De Camilli P, Baron R (2005) Dynamin forms a Src kinase-sensitive complex with Cbl and regulates podosomes and osteoclast activity. Mol Biol Cell 16:3301–3313
106. Hartig SM, Ishikura S, Hicklen RS, Feng Y, Blanchard EG, Voelker KA, Pichot CS, Grange RW, Raphael RM, Klip A, Corey SJ (2009) The F-BAR protein CIP4 promotes GLUT4 endocytosis through bidirectional interactions with N-WASp and dynamin-2. J Cell Sci 122:2283–2291
107. Zhao L, Shi X, Li L, Miller DJ (2007) Dynamin 2 associates with complexins and is found in the acrosomal region of mammalian sperm. Mol Reprod Dev 74:750–757
108. Okamoto PM, Herskovits JS, Vallee RB (1997) Role of the basic, proline-rich region of dynamin in Src homology 3 domain binding and endocytosis. J Biol Chem 272:11629–11635
109. Cao S, Yao J, Shah V (2003) The proline-rich domain of dynamin-2 is responsible for dynamin-dependent in vitro potentiation of endothelial nitric-oxide synthase activity via selective effects on reductase domain function. J Biol Chem 278:5894–5901
110. Sengar AS, Wang W, Bishay J, Cohen S, Egan SE (1999) The EH and SH3 domain Ese proteins regulate endocytosis by linking to dynamin and Eps15. EMBO J 18:1159–1171
111. Kamioka Y, Fukuhara S, Sawa H, Nagashima K, Masuda M, Matsuda M, Mochizuki N (2004) A novel dynamin-associating molecule, formin-binding protein 17, induces tubular membrane invaginations and participates in endocytosis. J Biol Chem 279:40091–40099
112. Tsujita K, Suetsugu S, Sasaki N, Furutani M, Oikawa T, Takenawa T (2006) Coordination between the actin cytoskeleton and membrane deformation by a novel membrane tubulation domain of PCH proteins is involved in endocytosis. J Cell Biol 172:269–279
113. Kharbanda S, Saleem A, Yuan Z, Emoto Y, Prasad KV, Kufe D (1995) Stimulation of human monocytes with macrophage colony-stimulating factor induces a Grb2-mediated association of the focal adhesion kinase pp 125FAK and dynamin. Proc Natl Acad Sci USA 92:6132–6136
114. Yoon SY, Koh WS, Lee MK, Park YM, Han MY (1997) Dynamin II associates with Grb2 SH3 domain in Ras transformed NIH3T3 cells. Biochem Biophys Res Commun 234:539–543
115. Gorska MM, Cen O, Liang Q, Stafford SJ, Alam R (2006) Differential regulation of interleukin 5-stimulated signaling pathways by dynamin. J Biol Chem 281:14429–14439
116. Xin X, Rabiner CA, Mains RE, Eipper BA (2009) Kalirin12 interacts with dynamin. BMC Neurosci 10:61
117. Bhattacharya R, Kang-Decker N, Hughes DA, Mukherjee P, Shah V, McNiven MA, Mukhopadhyay D (2005) Regulatory role of dynamin-2 in VEGFR-2/KDR-mediated endothelial signaling. FASEB J 19:1692–1694
118. Rasmussen RK, Rusak J, Price G, Robinson PJ, Simpson RJ, Dorow DS (1998) Mixed-lineage kinase 2-SH3 domain binds dynamin and greatly enhances activation of GTPase by phospholipid. Biochem J 335:119–124
119. Krendel M, Osterweil EK, Mooseker MS (2007) Myosin 1E interacts with synaptojanin-1 and dynamin and is involved in endocytosis. FEBS Lett 581:644–650
120. Pizzato M, Helander A, Popova E, Calistri A, Zamborlini A, Palu G, Gottlinger HG (2007) Dynamin 2 is required for the enhancement of HIV-1 infectivity by Nef. Proc Natl Acad Sci USA 104:6812–6817
121. Icking A, Matt S, Opitz N, Wiesenthal A, Muller-Esterl W, Schilling K (2005) NOSTRIN functions as a homotrimeric adaptor protein facilitating internalization of eNOS. J Cell Sci 118:5059–5069

122. Wan KF, Sambi BS, Frame M, Tate R, Pyne NJ (2001) The inhibitory gamma subunit of the type 6 retinal cyclic guanosine monophosphate phosphodiesterase is a novel intermediate regulating p42/p44 mitogen-activated protein kinase signaling in human embryonic kidney 293 cells. J Biol Chem 276:37802–37808
123. Park JB, Lee CS, Lee HY, Kim IS, Lee BD, Jang IH, Jung YW, Oh YS, Han MY, Jensen ON, Roepstorff P, Suh PG, Ryu SH (2004) Regulation of phospholipase D2 by GTP-dependent interaction with dynamin. Adv Enzyme Regul 44:249–264
124. Okamoto PM, Gamby C, Wells D, Fallon J, Vallee RB (2001) Dynamin isoform-specific interaction with the shank/ProSAP scaffolding proteins of the postsynaptic density and actin cytoskeleton. J Biol Chem 276:48458–48465
125. Bruzzaniti A, Neff L, Sandoval A, Du L, Horne WC, Baron R (2009) Dynamin reduces Pyk2 Y402 phosphorylation and SRC binding in osteoclasts. Mol Cell Biol 29:3644–3656
126. Lundmark R, Carlsson SR (2003) Sorting nexin 9 participates in clathrin-mediated endocytosis through interactions with the core components. J Biol Chem 278:46772–46781
127. Haberg K, Lundmark R, Carlsson SR (2008) SNX18 is an SNX9 paralog that acts as a membrane tubulator in AP-1-positive endosomal trafficking. J Cell Sci 121:1495–1505
128. Rufer AC, Rumpf J, von Holleben M, Beer S, Rittinger K, Groemping Y (2009) Isoform-selective interaction of the adaptor protein Tks5/FISH with Sos1 and dynamins. J Mol Biol 390:939–950
129. Bertelsen V, Breen K, Sandvig K, Stang E, Madshus IH (2007) The Cbl-interacting protein TULA inhibits dynamin-dependent endocytosis. Exp Cell Res 313:1696–1709
130. Gomez TS, Hamann MJ, McCarney S, Savoy DN, Lubking CM, Heldebrant MP, Labno CM, McKean DJ, McNiven MA, Burkhardt JK, Billadeau DD (2005) Dynamin 2 regulates T cell activation by controlling actin polymerization at the immunological synapse. Nat Immunol 6:261–270