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Review

Dynamin 2 in Charcot-Marie-Tooth Disease

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Charcot-Marie-Tooth disease (CMT) is an inherited neuronal disorder, and is induced by mutations of various genes associated with intracellular membrane traffic and cytoskeleton. A large GTPase, dynamin, which is known as a fission protein for endocytic vesicles, was identified as a gene responsible for dominant-intermediate CMT type 2B (DI-CMT2B). Of these mutants, the PH domain, which is required for interaction with phosphoinositides, was mutated in several families. Interestingly, the expression of a deletion mutant, 551Δ3, did not impair endocytosis, but induced abnormal accumulation of microtubules. Recent evidence has shown that dynamin 2 regulates the dynamic instability of microtubules, and 551Δ3 lacks this function. We propose a model for the regulation of the dynamic instability of microtubules by dynamin 2 and discuss the relationship between dynamin 2 and CMT.

Key words: neuropathy, Charcot-Marie-Tooth disease, membrane traffic, dynamin, microtubules

Charcot-Marie-Tooth diseases (CMT) are hereditary motor and sensory neuropathies that affect the peripheral nervous system. The CMT fall into 2 main groups. CMT type 1 includes demyelinating forms of the disease in which nerve conduction velocities (NCVs) are reduced; CMT type 2 includes axonal forms in which NCVs are normal, but conduction amplitudes are decreased [1]. There are also dominant intermediate (DI) subtypes of CMT, denoted DI-CMTA, DI-CMTB, DI-CMTC, and DI-CMTD, that are characterized by both axonal and demyelinating NCVs [2–5].

Depending on the gene affected and the type of mutation, functional deficits in either Schwann cells or neurons or both lead either directly or via disturbed Schwann cell-axon interactions to axonal atrophy and disability. The genes affected include motor proteins, structural proteins and others [1]. Of these, dynamin 2 has been identified as a gene responsible for DI-CMTB [6]. Dynamin is known as a fission protein for intracellular transport vesicles. Dynamin 2 is a ubiquitously expressed isoform, dynamin 1 is neuron-specific, and dynamin 3 is highly expressed in the brain, testis, lung and heart [7]. All dynamin isoforms are considered to act as fission proteins through their GTPase activity. Several mutations of dynamin 2 were found in CMT patients, and these mutations were concentrated in its Pleckstrin homology (PH) domain, which is required for binding to phosphoinositides.

Recently, we reported that dynamin 2 is required for the dynamic instability of microtubules, and a dynamin 2 mutant, which was found in CMT patients, impaired its microtubule-associated function [8]. As the clinical phenotype was described by others [9], we will focus on the function of dynamin and its association with clinical phenotypes.

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Dynamin and Its History

The Drosophila melanogaster mutant shibire (shi^{ts}), a temperature-sensitive paralytic mutant, was known [10] long before the discovery of mammalian dynamin. The paralysis that occurred in these flies resulted from the depletion of synaptic vesicles in neurons. Ultrastructural analysis of shi^{ts} mutant flies revealed an accumulation of endocytic pits at the presynaptic plasma membrane of the neurons [11] and in other cells [12]. Thus, the linkage between the shibire gene in endocytosis have been well established.

Mammalian dynamin was originally isolated from the bovine brain as a microtubule-binding protein [13]. Purified dynamin bound and interconnected microtubules [13] and supported microtubule gliding [14]. The amino acid sequence of dynamin, which contained 3 consensus elements characteristic of GTP-binding proteins, suggested that it is a GTPase [15]. As suspected, dynamin showed GTPase activity, which is highly stimulated by the presence of microtubules [16].

Following the identification of mammalian dynamin, rat brain dynamin and the Drosophila shibire gene were cloned and sequenced successively [15, 17], and considerably high homology between the primary structures of the 2 molecules was revealed (66% identity, 78% similarity). This finding immediately made dynamin a major topic of endocytosis research. Soon thereafter, endocytosis was examined in COS and HeLa cells overexpressing mutant dynamin, and it was found that endocytosis was blocked at an intermediate stage in these cells [18, 19].

Mammalian brain dynamin was exclusively expressed in neurons [20], preferentially after postnatal day 7 [21]. The neuron-specific isoform is termed dynamin 1, since 2 other isoforms with different tissue distributions have been identified. Dynamin 2 is expressed ubiquitously [22], and dynamin 3 is highly expressed in the brain, testis, lung and heart [23]. Dynamin isoforms were highly homologous to each other. The molecular mechanisms of dynamin-dependent endocytosis in mammals have been studied using mainly dynamin 1 and 2.

Molecular Mechanisms of Dynamin in Endocytosis

All the dynamin isoforms share 5 significant characteristic domains (Fig. 1). These include a highly conserved N-terminal GTPase domain, a middle domain that binds to γ-tubulin [24], a PH domain that interacts with phosphoinositides such as phosphinositide-4, 5-diphosphate ($PI(4, 5)P_2$) [25], and the GTPase-effector domain (GED). The proline/arginine-rich domain (PRD) at the C-terminus, which varies considerably between dynamin isoforms, mediates interaction with various SH3-domain-containing endocytic proteins, such as amphiphysin 1 [26, 27], endophilin [28], intersectin [29], and sorting nexin 9 [30]. Actin-binding proteins, such as cortactin and Abp1, also bind to PRD [31, 32].

Dynamin self-assembles, or assembles with a binding partner molecule into ring structures *in vitro* [27, 33]. Furthermore, in the presence of liposomes, dynamin polymerizes on the lipid bilayer, deforms the lipid membranes into narrow tubules, and constricts the lipid tubules to fragmentation upon GTP-hydrolysis [34, 35]. These properties of dynamin strongly support its role in the fission process of endocytic pits. On the plasma membrane, dynamin polymerizes into rings at the neck of deeply invaginated endocytic pits [36], and by conformational change that coincides with GTP hydrolysis, dynamin rings constrict the endocytic pits to fission [35, 37, 38]. This mechanism of action of dynamin in the fission process is referred to as the pinchase model. Another model in which conformational change of dynamin causes the extension of the dynamin spirals to pop off of the

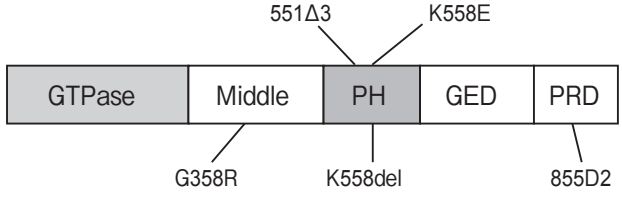

Fig. 1 Schematic representation of dynamin 2 indicating functional domains and mutation sites found in CMT patients. The illustrated functional domains in dynamin 2 are as follows: GTPase domain, middle domain, Pleckstrin homology domain (PH), GTPase-effector domain (GED) and proline-rich domain (PRD). The role of each domain is described in the text. The mutation sites are based on Claeys *et al.* (2009) [9].

endocytic pits, which is referred to as the poppase model, has been proposed [34]. In either case, dynamin functions as a GTP hydrolysis-driven mechanoenzyme. The enzymatic characteristics of dynamin GTPase activity that are stimulated by self-assembly [39], by interaction with membrane lipids such as PI(4, 5)P_2 via the PH domain [40], or by interaction with a subset of SH3-domain-containing molecules via PRD [27] are favorable for these models.

The interaction of dynamin with SH3-domain-containing proteins may represent a mechanism for facilitating dynamin's fission reaction with other factors. For example, through the interaction with BAR-domain-containing proteins such as amphiphsyin or endophilin, the sensing or inducing of membrane curvature by its BAR domain is synchronized with the fission reaction by dynamin [27, 41]. Through the interaction of dynamin with ABP1 or cortactin, actin dynamics would take place at the site of endocytosis. Treatment with Latrunculin B, an actin-monomer-sequestering agent that blocks fast actin polymerization, resulted in inhibition of the fission reaction, which implies the presence of actin dynamics in endocytsis [41].

Dynamin 1 is phosphorylated by several kinases including PKC and CDK5, and is dephosphorylated by calcineurin. Endocytosis is enhanced in the presence of roscovitine, a CDK5 inhibitor, indicating that CDK5-dependent phosphorylation of dynamin 1 negatively regulates this process. CDK5 phosphorylates not only dynamin 1 but also amphiphsyin 1, its binding partner in endocytosis, and the interaction between dynamin 1 and amphiphysin 1 is inhibited by the phosphorylation [42].

Dynamin1 single knockout mice were viable and able to form functional synapses in which membrane invaginations were accumulated and capped by clathrin-coated pits. Synaptic vesicle endocytosis was severely impaired only during strong stimulation but resumed efficiently when the stimulus was terminated, indicating that dynamin 1-dependent endocytosis is needed for a high level of neuronal activity to occur [43]. In dynamin 1 and dynamin 2 double-knockout cells, actin-nucleating proteins, actin, and BAR domain proteins accumulate at the base of arrested endocytic clathrin-coated pits with long tubular necks. These results suggest that dynamin plays a role in coordinating the action of these proteins with the fission reaction induced by dynamin [44].

Cytoskeleton and Dynamin

Dynamin is implicated in the formation of actin-rich structures, such as podosomes [45], invadopodia [46], lamellipodia and dorsal membrane ruffles [7, 31, 47], phagocytic cups [48], and actin comets [49, 50]. Consistent with the link between dynamin and the actin cytoskeleton in cellular functions, molecular interactions between dynamin and a variety of actin-binding proteins, including profilin [51], cortactin [31], syndapin [52], and Abp1 have been reported. Most of these studies emphasize the function of the actin cytoskeleton in dynamin-dependent vesicle formation, but some indicate the direct involvement of dynamin in the regulation of the actin cytoskeleton. For example, dynamin 2 observed in the actin comet is not restricted at the vesicle-actin comet interface, but also extends along the length of the comet tails [50]. The assembly and remodeling of actin filaments by dynamin 2, through an interaction with cortactin, has been demonstrated by *in vitro* experiments [53, 54], and this ability of dynamin may be implicated in the regulation of supramolecular F-actin arrays *in vivo*.

Although dynamin1 was originally identified as a microtubule-binding protein [13], and its GTPase activity was stimulated by microtubules [16, 55] as mentioned, the physiological significance of the interaction in the cell remained to be clarified. In mitotic cells, dynamin 2 was concentrated at the microtubule bundle at the spindle midzone and the intercellular bridge in cytokinesis [56]. The middle domain of dynamin 2 binds to γ-tubulin, and they colocalize at the centrosome, where dynamin 2 is thought to play a role in centrosome cohesion [24]. Consistent with these observations during mitosis, dynamin is enriched in spindle midbody extracts [56].

Novel Role of Dynamin in Microtubule Dynamics

We recently reported that dynamin 2 regulates the dynamic instability of microtubules [8]. The structure and dynamics of microtubules are described in other reviews [57–59]. Briefly, a microtubule typically comprises 13 protofilaments, which form the wall of a tube. Each of the protofilaments consists of α/β

tubulin heterodimers. GTP-bound tubulin is added onto the plus-tips of microtubules, and the hydrolysis of GTP induces conformational change in the tubulin dimer, which causes microtubule depolymerization. This dynamic instability of microtubules is regulated by many factors [60].

As mentioned above, dynamin was originally identified as a microtubule-associated protein, but its biological significance remained unclear. We found that dynamin 2 was localized onto microtubules *in vivo*, suggesting that dynamin has a role in the regulation of microtubules. In dynamin 2-depleted cells, no apparent alteration at "bulk" microtubules was found in "fixed cells." Interestingly, however, acetylated tubulin and de-tyrosinated tubulin, which are markers of stable microtubules, were significantly increased. Using live cell imaging, the dynamic instability of microtubules in dynamin 2-depleted cells was apparently decreased compared with control cells. Quantitative analysis revealed that the rates of growth and shortening were not significantly changed, but the duration of growth and shortening was significantly reduced in dynamin 2-depleted cells. This implies that dynamin 2 is not required for the growth or shortening machinery itself, but is necessary for the initiation or maintenance of these dynamics.

Next, we examined the biological significance of the dynamic instability regulated by dynamin 2. Microtubules are required for the proper localization and transport of intracellular organelles, and dynamic instability of microtubules seems to be required for the search-and-capture of its target cargoes [59, 61, 62]. The plus tips of microtubules search its cargoes by repetitive growing and shortening, and when the plus tips encounter its cargoes, the cargoes are caught and moved toward the minus end of the microtubules. Dysfunction of microtubule dynamics impairs organelle transport and subsequently induces a lack of formation of the Golgi and lysosomal degradation.

In dynamin 2-depleted cells, both the pericentriolar localization of endosomes and the formation of Golgi were impaired. Recycling endosomes and Golgi cisternae were scattered all around the cell, implying that microtubule-dependent intracellular transport was impaired. Interestingly, this was not observed by means of the expression of the dynamin 2-dominant negative mutant (K44A), which is a GTPase-negative mutant. As the expression of dynamin 2 K44A inhibits dynamin-dependent intracellular traffic, the dynamic instability of microtubules regulated by dynamin 2 seems to be independent of the GTPase activity, and seems not to be a secondary effect of the impairment of intracellular traffic. Similar results have been reported by others in the regulation of centrioles [24].

Thus, the major question is how dynamin regulates the dynamic instability of microtubules. Although the molecular mechanism remains to be elucidated, we illustrate the current model of the regulation of the dynamic instability of microtubules by dynamin in Fig. 2. MCAK, a member of the kinesin-13 family, was the first identified microtubule depolymerizing factor [63, 64]. Although MCAK is a kinesin, it does not move in a directed manner on the lattice. Rather, MCAK targets by a "diffusion and capture" mechanism in which it is weakly associated with the lattice [65]. Many proteins were associated with microtubule polymerization. Of these, the most famous polymerization factor is XMAP215, and other MAPs including tau and doublecortin regulate polymerization [60, 66]. The common model of the regulation of dynamic instability is focused on the plus-tips of microtubules, including EB1, CLASPs and CLIP170. We propose that dynamin 2 may act as a "ratchet" by rolling up the microtubules and may limit the range of MCAK movements (Fig. 2A). In the absence of the dynamin "ratchet", MCAK may diffuse all along the full-length microtubules, and as a result, inefficient regulation of microtubule dynamics followed by accumulation of stable microtubules may occur (Fig. 2B). Of course, as this model is not based on biochemical experiments, further experiments regarding the molecular mechanisms are required.

Dynamin and Disease

Dynamin has recently been identified as a disease-responsible gene in multiple diseases [6, 67]. In DI-CMT patients, several mutations were found in the PH domain of dynamin 2 (Fig. 2). The PH domain is responsible for the interaction with phospholipids, which is followed by the proper localization and/or activation of the proteins. Dynamin binds specifically to $PI(4, 5)P_2$ through the PH domain, and this interaction is required for the localization of dynamin onto the membrane [68]. Thus, the PH domain is required

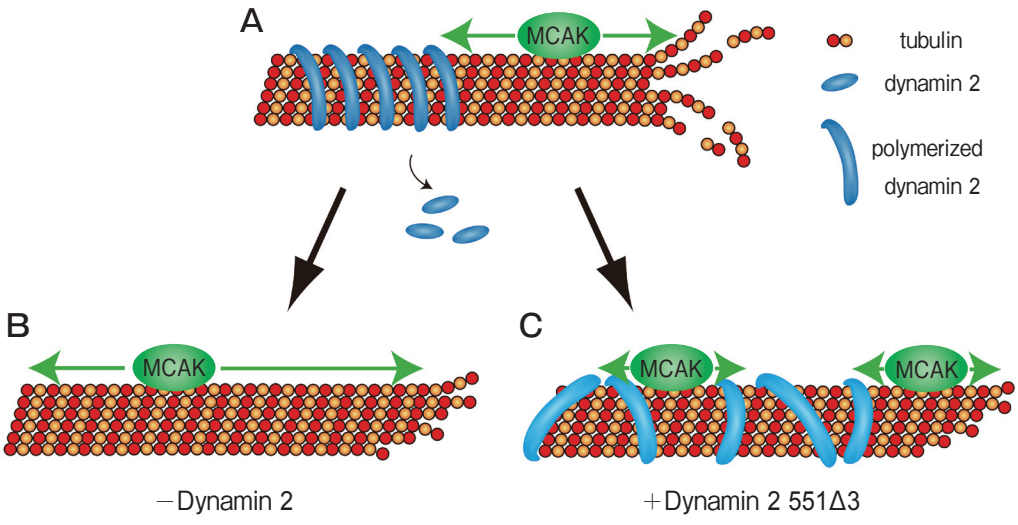

Fig. 2 Hypothetical models of dynamic instability of microtubules under the control of dynamin 2 and its mutant. Dynamin 2 polymerizes around microtubules and undergoes polymerization/depolymerization cycles. The microtubule depolymerization factor, MCAK, moves by lattice diffusion on microtubules [65]. Dynamin 2 may cause a limitation of the range of MCAK movements and induce proper dynamic instability of the microtubules (**A**). However, in the absence of dynamin 2, MCAK moves freely on a broad range of microtubules, and this causes a reduction in the frequency of depolymerization (**B**). A CMT mutant, 551Δ3, showed robust localization along the microtubules and may lack the proper polymerization or regulated depolymerization [8]. This may inhibit the localization or the movement of MCAK, resulting in the inhibition of microtubule depolymerization (**C**).

for the proper function of dynamin, and its deletion causes an endocytic defect [69].

Of the CMT mutants, K558E completely blocked dynamin-dependent endocytosis, as observed in a dominant-negative K44A mutant [8]. This suggests that the mutant K558E lacks interaction with PI(4, 5) P_2. Whereas another mutant, 551Δ3, did not block dynamin-dependent endocytosis, suggesting that the mutation did not affect the membrane localization of dynamin 2. Interestingly, however, internalized ligands were not localized around the perinuclear area in 551Δ3-expressing cells. Moreover, Golgi formation, which depends on microtubule-dependent transport, was also disturbed by the expression of 551Δ3, suggesting that microtubule-dependent transport was impaired by the expression of 551Δ3. As described above, we found that the depletion of dynamin 2 caused the accumulation of stable microtubules and the impairment of microtubule-dependent membrane transport. The expression of 551Δ3 also induced the accumulation of stable microtubules, suggesting that the dynamic instability of the microtubules was affected by the mutation 551Δ3.

Fig. 2C illustrates a hypothetical model of abnormal microtubule dynamic regulation by 551Δ3. As assessed by localization analysis, 551Δ3 showed robust localization onto microtubules, suggesting that the regulation of the localization onto microtubules was impaired in this mutant [8]. This abnormal localization may create some limitations for the movement of depolymerization factors.

All of the dynamin mutants found in CMT disease was found only in dynamin 2, not in dynamin 1. The expression level of dynamin 2 is less than that of dynamin 1, which is a brain-specific form. This may suggest that the function related to microtubules is not redundant between these dynamin isoforms. This suggestion was supported by recent reports showing that both dynamin 1 and dynamin 2 have individual functions in endocytosis, actin reorganization and other processes [7, 70]. A recent report has shown that dynamin 1 knockout was rescued by the overexpression of dynamin 3 but not of dynamin 2 [43]. This clearly shows that each dynamin isoform may have a distinct function in the neurons. Another possibility is that the major defect in DI-CMTB caused by the mutation of dynamin 2 occurs in Schwann cells rather than in neurons.

A point mutant, K558E, impaired the dynamin-dependent endocytosis, but another deletion mutant, 551Δ3, did not. This suggests that these mutants impair intracellular transport at distinct steps, that is, at the internalization step and at the transport step, respectively. The clinical phenotypes resemble each other, but are not identical in detail. For example, the number of neutrophils was decreased in patients with the K558E mutant, but not in those with 551Δ3 [6]. Recently, other dynamin mutants have been found in CMT type 2 [71], which is caused by defects in axonal transport. This is apparently a distinct phenotype from DI-CMTB, and this discrepancy should be elucidated at the molecular level in future investigations.

Other dynamin 2 mutants have been found in patients with centronuclear myopathy, which is characterized by the concentration of the nucleus in multinucleated myocytes [67]. The mutations were concentrated in the middle domain between the GTPase domain and the PH domain. This middle domain binds to γ-tubulin and regulates the structure of the centrosomes [24]. This function does not require GTPase activity, as observed in the regulation of microtubule dynamics. Future study could reveal the molecular mechanisms between the function of the middle domain and the clinical phenotypes resulted from the mutation of the domain.

Conclusion

Dynamin was originally found to be a microtubule-binding protein. We recently found that dynamin 2 regulates the dynamic instability of microtubules, and that a mutant found in CMT patients, 551Δ3, lacked the function for microtubules but not for endocytosis. In contrast, another mutant, K558E, lacked the function for endocytosis but not for microtubules. This reveals that these CMT mutants induce neuropathy by different cellular mechanisms.

There are many genes responsible for CMT disease, and many distinct intracellular processes are associated with the disease. Dynamin 2 was identified as one of the CMT-responsible genes, and there are some differences at the cellular level between K558E and 551Δ3. The phenotypical disorders also seem to be slightly different between these 2 mutations. For example, the number of neutrophils [6] was abnormal in patients carrying the K558E mutation, but not in patients carrying the 551Δ3 mutation. Given the current state of knowledge about dynamin and CMT, it is difficult to say whether the inhibition or activation of dynamin would be useful for dealing with these diseases. Further elucidation of the molecular mechanisms, including dynamin's role on the regulation of microtubules, could be required.

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