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Etiological Role of Dynamin in Charcot-Marie-Tooth Disease

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1. Introduction

Charcot–Marie–Tooth disease (CMT) is one of the most common inherited neuropathy, with estimated prevalence of 17 to 40 in 100,000 affected (Patzkó, & Shy, 2011). CMT is characterized by atrophy of muscle tissue and loss of touch sensation of limb, predominantly in the feet and legs, foot drop, and hammer toes. The most frequent initial symptoms include foot drop, claw toe, and muscle wasting in the hands. Symptoms in the advanced cases may include muscle waste in the hands and fore arms, neck and shoulder, vocal cords, which leads to scoliosis and malfunction in chewing, swallowing, or speaking.

The defective neurotransmission stems from either degradation of myelin sheath or breakdown of neuronal axon, which define primary forms of this disease, CMT type 1 and CMT type 2 respectively. CMT type 1 and CMT type 2 can be clinically distinguished based on nerve conduction velocity (NCV). Slow NCV (less than 38 m/s) is characteristic of demyelinating CMT type 1, and the average NCV is slightly below normal, but above 38 m/s in CMT type 2. In addition, dominant intermediate subtypes of CMT (DI-CMT) have been identified, which are characterized by NCVs overlapping both demyelinating and axonal range (25 - 45 m/s).

Number of genes and gene loci has been involved in the pathogenesis of CMT, and despite of diversity of the responsible genes, they are involved in common molecular pathways within Schwann cells and axons that cause these genetic neuropathies (Patzkó & Shy, 2011). CMT Type 1 primarily affects the myelin sheath, and is inherited as dominant, recessive or X-linked. Type 2 primarily affects the axon, and is either dominant or recessive. DI-CMT is classified type A (DI-CMTA), type B (DI-CMTB) type C (DI-CMTC), and type D (DI-CMTD) according to responsible genes and gene loci.

In this review, we focus on dynamin 2 and the mutations, which are responsible for DI-CMTB and axonal CMT type 2. We explain physiological role of dynamin 2 in the regulation of microtubules and propose possible pathogenesis of CMT attributed to dynamin 2 mutants.

2. Dyanmin2 mutation in CMT

As described above, three types of dominantly inherited CMT with intermediate NCV DI-CMT) are known. DI-CMTA was found in a large Italian family and it is linked to chromosome 10q24.1-q25.1 (Rossi et al., 1985; Verhoeven et al., 2001; Villanova et al., 1998),

but the responsible gene remains currently unknown. Two unrelated Midwestern-American and Bulgarian families with DI-CMT are linked to chromosome 1p34-p35, and it is classified as DI-CMTC (Jordanova et al., 2003b). In DI-CMTC, a mutation has been identified in tyrosyl-tRNA synthetase (YARS)(Jordanova et al., 2006).

Studies on DI-CMT in unrelated two large pedigrees originating from Australia and North America, has assigned the locus (DI-CMTB) to chromosome 19p12–13.2. (Kennerson et al., 2001; Zhu et al., 2003). Successively, Züchner and coworkers refined the locus of the two DICMTB families and additional Belgian family, and identified mutations in dynamin 2 (Züchner et al., 2005). The North-American family showed a 9-bp deletion of the 3′ end of exon 14 of DNM2, 1652_1659+1delATGAGGAGg which is predicted to result in a shift of the open reading frame leading to a premature stop codon (Lys550fs), and the production of an in-frame mRNA with predicted deletion of three amino acids (Asp551_Glu553del). The Australian family and the Belgian family affect the same amino acid residue of dynamin 2: Lys558. The Australian family carried a missense mutation in exon 15, 1672A→G, resulting in the amino acid substitution Lys558Glu. The Belgian family showed a deletion of a single amino acid, Lys558del (1672_1674delAAG). Dynamin mutations in DI-CMTB identified in the original report were restricted in its PH domain (Züchner et al., 2005, Fig. 2).

Subsequently, Claeys et al., analyzed the three original families and in three additional unrelated Spanish, Belgian and Dutch families with DI-CMTB and found two novel mutations in dynamin 2 (Claeys et al., 2009). They identified the novel missense mutation Gly358Arg (1072G4A) in exon 7 of dynamin 2 in the Spanish family, and the novel Thr855_Ile856del (2564_2569delCCATTA) mutation in exon 19 in the index patient of the Belgian family. These mutations are situated in the middle domain and proline-rich domain of dynamin 2, respectively (Fig. 2). Other mutations of dynamin 2 have been identified in CMT patients who present with symptoms typical of axonal CMT (CMT2)(Fabrizi et al., 2007; Bitoun et al., 2008). The later study identified a heterozygous three base-pair deletion located in exon 15 of dynamin 2 (1675_1677delAAA) which results in the loss of the highly conserved lysine 559 (Lys559del) located in the PH domain (Fig.2).

3. Overview of dynamin

Before mentioning possible pathogenesis of CMT caused by the mutation of dynamin 2, the key molecule will be outlined here. In addition to the biochemical characteristics of the molecule, when and how the protein has been identified and studied, or what has been known so far regarding to its functions, will be described below.

3.1 Identification of dynamin

Long before the discovery of mammalian dynamin, Drosophila melanogaster mutant shibire (shi^{ts}), a temperature-sensitive paralytic mutant, has been known (Grigliatti et al., 1973) Ultrastructural analysis of the neuromuscular junction of shi^{ts} mutant fly revealed depletion of synaptic vesicles and accumulation of endocytic pits at presynaptic plasma membrane of neurons (Kosaka & Ikeda, 1983). Thus, the paralysis of shi^{ts} mutant fly is caused by synaptic dysfunction due to blockage of synaptic vesicle endocytosis.

Mammalian dynamin was originally isolated from bovine brain as a microtubule-binding protein (Shpetner & Vallee, 1989). Purified dynamin bound and interconnected microtubules, and supported microtubule gliding (Shpetner & Vallee, 1989, Fig. 1).

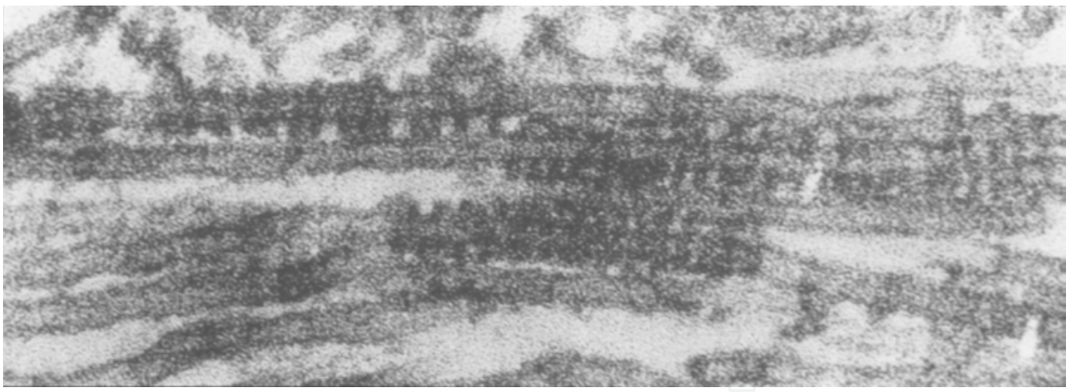

Fig. 1. Electron micrograph of dynamin polymerizing around microtubules.
Bundle of microtubules decorated with dynamin (from Shpetner & Vallee, 1989).

Following the identification, dynamin was cloned and sequenced (Obar et al., 1990). The amino acid sequence contained three consensus elements characteristic of GTP-binding proteins and suggested that it is a GTPase (Obar et al., 1990). As suggested, dynamin was turned out to be a GTPase, which was highly stimulated by the presence of microtubules (Shpetner & Vallee, 1992). Later on, Drosophila shibire gene was cloned and sequenced (Obar et al., 1990; van der Bliek et al., 1991), which revealed considerably high homology of mammalian dynamin and shibire gene product (66% identity, 78% similarity). This revelation immediately put dynamin in the central stage of endocytosis research. In a short while, endocytosis was examined in COS and HeLa cells overexpressing mutant dynamin, and it was found that an endocytosis is blocked at an intermediate stage (Herskovits et al., 1993; van der Bliek et al., 1993).

3.2 Dynamin Isoforms and their expression

The mammalian brain dynamin was exclusively expressed in neurons (Scaife & Margolis, 1990), preferentially after postnatal day 7 (Nakata et al., 1991). This neuron-specific isoform is termed dynamin 1 after two other isoforms with different tissue distributions were identified. Dynamin 2 is expressed ubiquitously (Cook et al., 1994), and dynamin 3 is expressed highly in brain, testis, lung and heart (Nakata et al., 1993).

3.3 Domain structure of dynamin

Dynamin isoforms were highly homologous, and all the dynamin isoforms share five characteristic domains (Fig. 2). They include highly conserved N-terminal GTPase domain, middle domain that binds to γ-tubulin (Thompson et al., 2004), pleckstrin homology domain (PH) that serves as binding motif for phophinositide-4, 5-bisphosphate (PIP_2)(Barylko et al., 1998), and GTPase effector domain (GED). C-terminal Proline/arginine -rich domain (PRD) considerably varies between dynamin isoforms, and mediates interaction with various SH3-domains containing molecules, which include endocytic proteins amphiphysin 1 (David et al., 1996; Yoshida et al., 2004), endophilin (Ringstad et al., 1997), intersectin (Zamanian et al., 2003), and sorting nexin 9 (Ramachandran & Schmid, 2008). Actin binding proteins, such as cortactin and Abp1, also contain SH3 domain and bind to dynamin PRD (McNiven et al., 2000; Kessels et al., 2001).

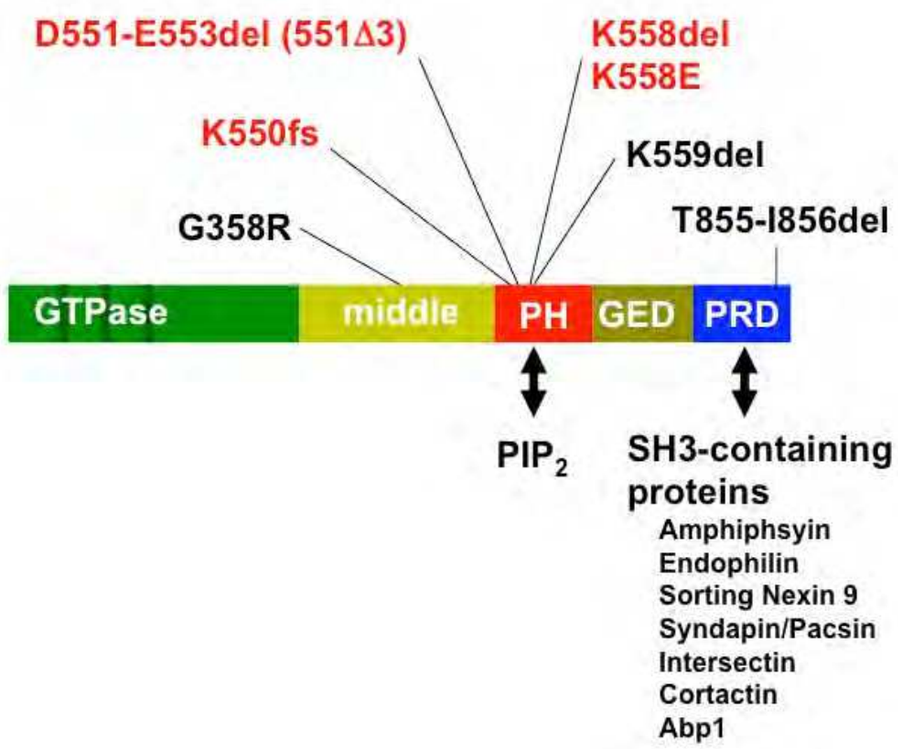

Fig. 2. Domain structure of dynamin and its mutation cites identified in CMT patients
All dynamin isoforms contains five functional domains. Reported mutations found in CMT patients are shown. Among these, four mutations indicated in red are reported in the first study on dynamin mutation in CMT (Züchner et al., 2005). Counterparts of dynamin's binding motifs, PH and PRD, are also shown. GTPase: GTPase domain, middle: middle domain, PH: pleckstrin homology domain, GED: GTPase effector domain, PRD: Proline/arginine -rich domain, PIP_2: phophinositide-4, 5-bisphosphate.

3.4 Function of dynamin in endocytosis

Dynamin self-assembles, or assembles with a binding partner molecule into rings and spirals *in vitro* (Hinshaw & Schmid, 1995; Takei et al., 1999). Furthermore, in presence of lipodsomes, dynamin polymerizes on the lipid membranes and deform them into narrow tubules, and constricts the lipid tubules to fragments upon GTP-hydrolysis (Sweitzer & Hinshaw, 1998; Takei et al., 1998; Stowell et al., 1999). This biophysical property of dynamin seems to support its role in the fission of endocytic pits in endocytosis.

Physiologically, dynamin assembles into rings and spirals at the neck of deeply invaginated endocytic pits formed on the plasma membrane (Takei et al., 1995), and conformation of the polymerized dynamin is changed upon GTP hydrolysis providing a driving force to squeeze the neck to membrane fission (Sweitzer & Hinshaw, 1998; Takei et al., 1998; Marks et al., 2001; Roux et al., 2006; Ramachandran & Schmid, 2008)(Fig.3). This mechanism of action of dynamin in endocytosis is referred as pinchase model (McNiven, 1998). Another model, in which conformational change of dynamin cause the extension of the dynamin spirals to pop off of the endocytic pit, is also proposed as popase model (Stowell et al., 1999). In either case, dynamin functions as a GTPase-driven mechanoenzyme in endocytosis.

Dynamin GTPase activity is stimulated by self-assembly (Warnock et al., 1996), by PH domain-mediated interaction with membrane lipids such as PIP_2 (Lin et al., 1997), or by PRD-mediated interaction with subset of SH3 domain-containing proteins (Yoshida et al., 2004). This enzymatic characteristic of dynamin would be favorable for its function as a mechanochemical enzyme in endocytosis.

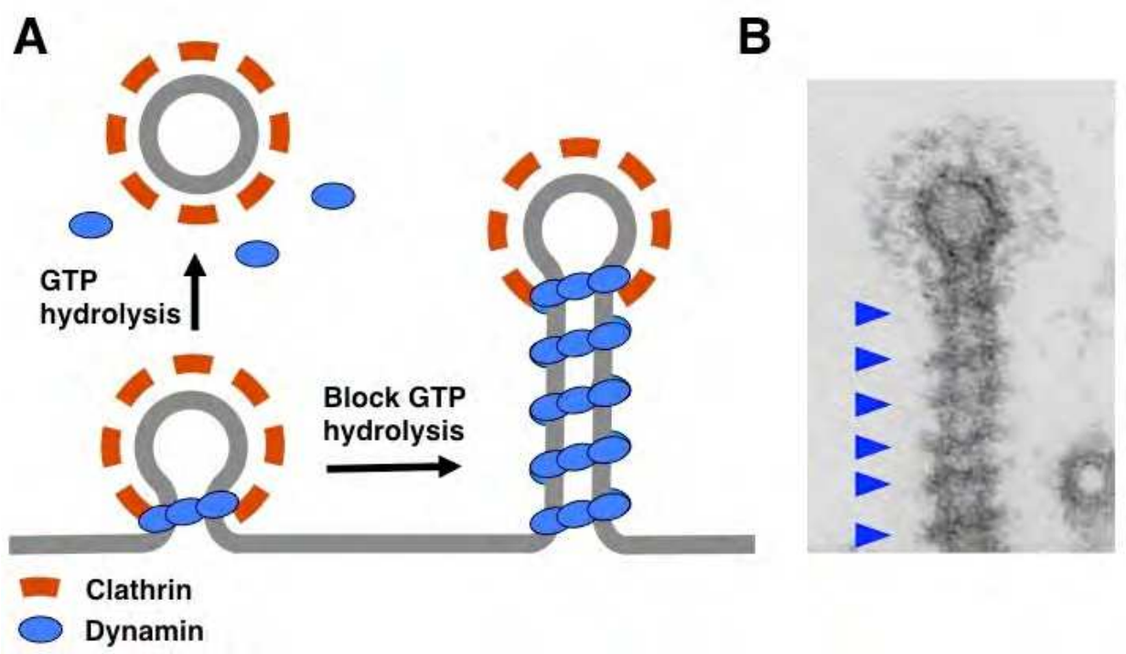

Fig. 3. Function of domain in endocytosis A: Dynamin assembles into rings at the neck of deeply invaginated endocytic pits formed on the plasma membrane. Conformational change of the polymerized dynamin upon GTP hydrolysis provides a driving force to squeeze the endocytic pit to membrane fission (left). Experimentally inhibiting the GTP hydrolysis results in overpolymerization of dynamin around elongated endocytic pit (middle).
B: Electron micrograph of elongated endocytic pit decorated with dynamin (arrowheads, from Takei et al., 1995)

Dynamin PRD interacts with various SH3 domain-containing endocytic proteins enriched in the synapse, including amphiphysin 1 (David et al., 1996; Takei et al., 1999; Yoshida et al., 2004), endophilin (Farsad et al., 2001), sorting nexin 9 (Ramachandran & Schmid, 2008; Shin et al., 2008), syndapin (Kessels et al., 2004), and intersectin (Yamabhai et al., 1998). Such interactions may be utilized to incorporate various functional molecules synchronously required for endocytosis. For example, by interacting with amphiphysin or endophilin, BAR domain–containing endocytic proteins, BAR domain's function of sensing or inducing membrane curvature would be synchronized with dynamin's fission activity (Yoshida et al., 2004; Itoh et al., 2005). By interacting with Abp1 or cortactin, actin dynamics would take place at the site of endocytosis (Kessels et al., 2001). Treatment with Latrunculin B, actin monomer-sequestering agent that blocks fast actin polymerization, results in the inhibition of fission reaction, supporting an implication of actin dynamics in endocytosis (Itoh et al., 2005).

Dynamin 1 is phosphorylated by several kinases including PKC and CDK5, and dephosphorylated by carcinerurin. Dynamin-dependent endocytosis is enhanced in presence of Roscovitine, CDK5 inhibitor, indicating that CDK5-dependent phosphorylation of dynamin1 negatively regulates endocytosis. CDK5 phosphorylates not only dynmain1 but also amphiphsyin1, its biding partner in endocytosis, and phosphorylation of these molecules decreases the binding affinity of these endocytic molecules (Tomizawa et al., 2003).

3.5 Implication of dynamin in actin dynamics

Involvement of dynamin in the regulation of actin dynamics is based largely on studies using dynamin 2, a ubiquitous isoform. Dynamin 2 is enriched in variety of actin-rich structures, such as podosomes (Ochoa et al., 2000), invadopodia (Baldassarre et al., 2003), lamellipodia and dorsal membrane ruffles (Cao et al., 1998; Krueger et al., 2003; McNiven et al., 2000), phagocytic cups (Gold et al., 1999), and Listeria actin comets (Lee & De Camilli, 2002; Orth et al., 2002). Several studies suggest functional implication of dynamin GTPase in actin dynamics. Expression of dynamin K44A, a GTPase defective mutant, reduces the formation of actin comets (Lee & De Camilli, 2002; Orth et al., 2002), podosomes (Ochoa et al., 2000; Bruzzaniti et al., 2005), and drastically changes cell shape (Damke et al., 1994).

Consistent with the localization and implication of dynamin in these actin-rich structures, molecular interactions of dynamin 2 with actin (Gu et al., 2010) and actin-regulating proteins such as Abp1 (Kessels et al., 2001), profilin (Witke et al., 1998) and cortactin (Schafer et al., 2002; McNiven et al., 2000) have been reported. Some studies emphasizes that these interactions represent mechanisms to incorporate actin dynamics in dynamin-dependent endocytosis. For example, interaction between dynamin 2 and cortactin, SH3-domain containing actin binding protein that binds also F-actin and actin-regulating Arp2/3 complex (Ammer & Weed, 2008), is associated with clathrin and dynamin-dependent endocytosis (Krueger et al., 2003; Cao et al., 2003; Zhu et al., 2005). On the other hand, however, the same dynamin-cortactin interaction is considered as a mechanism to recruit dynamin to the site of actin dynamics in other studies (McNiven et al., 2000; Schafer et al., 2002; Mooren et al., 2009; Yamada et al., 2009).

Assembly and remodeling of actin filaments by dynamin 2, through an interaction with cortactin, has been investigated by in vitro experiments (Schafer et al., 2002; Mooren et al., 2009). In their recent study, they demonstrated that, in the presence of dynamin, GTP led to remodeling of actin filaments in vitro via the actin-binding protein cortactin (Mooren et al., 2009). As the mechanism of the actin regulation, they suggests that GTP hydrolysis-induced conformational change within dynamin is transduced to cortactin, which in turn alters orientation of the F-actin so that actin's sensitivity to cofilin, an actin depolymerizing factor, is increased (Mooren et al., 2009). However, as interactions between dynamin's PRD and cortactin's SH3 domain does not require GTP binding nor hydrolysis by dynamin, it remains uncertain how GTP hydrolysis dependent conformational change within dynamin might be transmitted to cortactin. More recently, direct interaction between dynamin and actin has been identified, and it was proposed that the interaction leads to release of gelsolin, an actin capping protein, from the actin filament (Gu et al., 2010). However, it remains unclear how dynamin GTPase activity is utilized to alter the affinity of F-actin to the actin regulatory factor.

4. Implication of dynamin in microtubule dynamics

As described above, dynamin 1 was originally identified as a microtubule-binding protein (Shpetner & Vallee, 1989), and its GTPase activity was stimulated by microtubules (Shpetner & Vallee, 1989; Maeda et al., 1992). However, physiological significance of the dynamin-microtubule interaction has not been elucidated yet.

The association between dynamin and microtubules was recently investigated in relation to mitosis, in which tubulin plays a role as in mitotic spindle and centrosome. In mitotic cells, dynamin 2 was concentrated at microtubule bundles at mitotic spindle (Ishida et al., 2011), spindle midzone, and intercellular bridge in cytokinesis (Thompson et al., 2002). 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 (Thompson et al., 2004). Consistent with such observation, dynamin is enriched in spindle midbody extracts (Thompson et al., 2002).

4.1 Dynamin CMT mutant 551Δ3 impairs microtubule dynamics

Dynamin's role of on microtubules at interphase was incidentally revealed as a result of our recent investigation on dynamin mutations found in CMT patents (Tanabe & Takei 2009).

In order to elucidate molecular pathogenesis of dynamin 2-cused CMT disease, we overexpressed dynamin CMT mutants, 551Δ3 and K558E, in COS-7 cells, and examined the dynamin's role on microtubules. Endocytosis, which was assessed by transferrin uptake, was completely blocked by K558E as reported before (Züchner et al., 2005). Interestingly, 551Δ3 did not block endocytosis, but the transferrin-containing early and recycling endosomes no longer accumulated at the perinuclear region suggesting dysfunction of microtubule-dependent vesicular transport in dynamin 2-caused CMT (Fig.4).

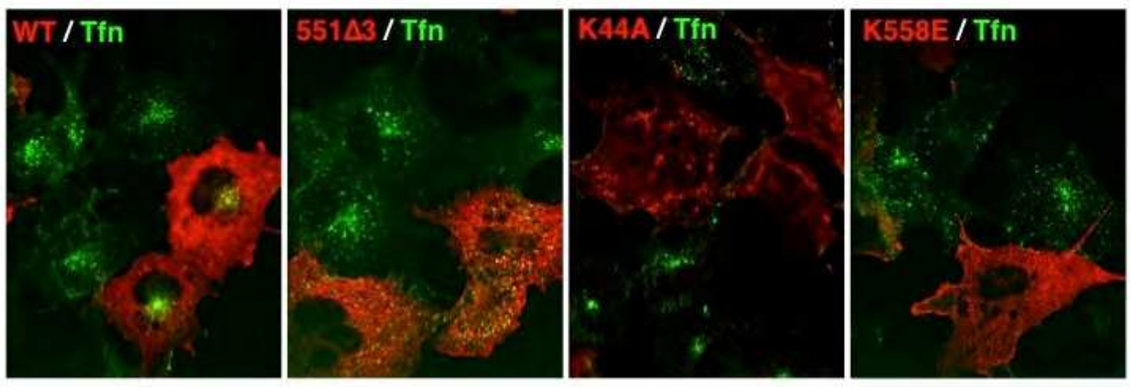

Fig. 4. Endocytosis of transferrin in dynamin 2 mutant expressing cells. COS-7 cells transfected with the indicated constructs were incubated with Alexa Fluor 488–transferrin for 30 min, and exogenous dynamin was stained by immunofluorescence (red). Note that transferrin (green) is internalized in 551Δ3 expressing cells, but the transferrin is not accumulated at perinuclear region (second panel from the left) in contrast to dynamin WT expressing cells (left). Endocytosis is blocked in dynamin K44A and K558E expressing cells (right two panels). (from Tanabe & Takei, 2009)

As mentioned above, dynamin was originally identified as a microtubule-associated protein (Shpetner & Vallee, 1989). Both dynamin 1 and dynamin 2 polymerizes around microtubules, and the interactions lead to the stimulation of dynamin GTPase activity (Maeda et al., 1992; Warnock et al., 1997). Consistently, in cells, subpopulation of dynamin 2 is present at microtubules in addition to the plasma membrane and cytosol. Localization of dynamin at microtubules become more prominent in 551Δ3 expressing cells (Züchner et al., 2005; Tanabe & Takei, 2009), probably because of its increased affinity to microtubules.

Microtubules can be very stable or highly dynamic depending on the cell cycle stage, and on position of the cell within the organism (Schulze & Kirschner, 1987). Microtubule typically comprises 13 protofilaments, which are consisted of α/β tubulin heterodimers. The tubulin dimers can depolymerize as well as polymerize, and microtubules can undergo rapid cycles of assembly and disassembly. GTP-bound tubulin is added onto plus-tips of microtubules and hydrolysis of GTP induces conformational change in tubulin dimer, which induces microtubule depolymerization. This dynamic instability of microtubules is regulated by many factors (Howard & Hyman, 2007).

Stable microtubules are subject to acetylation (Piperno et al., 1987; Westermann & Weber, 2003), thus they can be distinguished from dynamic microtubules by measuring acetylated tubulin. Acetylated tubulin was massively increased in 551Δ3 expressing cells compared to WT dynamin (Fig.5), in spite of the protein expression levels were unchanged, indicating that the 551Δ3 mutation of dynamin 2 impairs dynamic instability of microtubules.

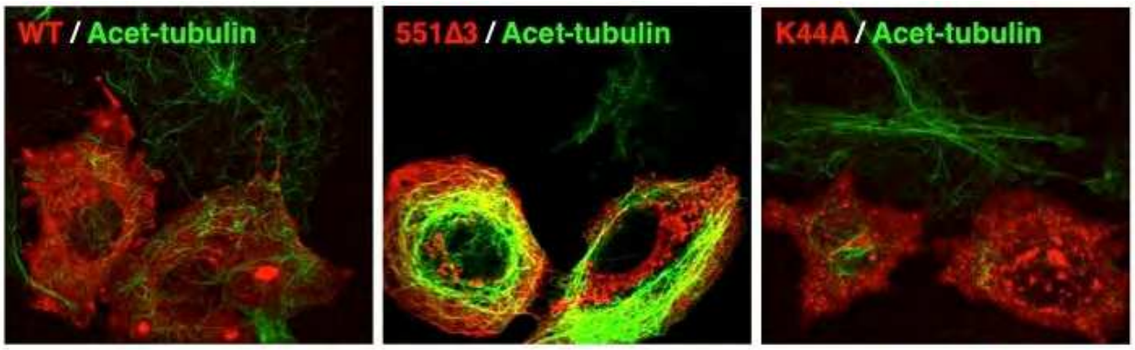

Fig. 5. Expression of 551Δ3 dynamin 2 mutant causes accumulation of acetylated tubulin. COS-7 cells were transfected with the indicated dynamin constructs and visualized by immunofluorescence for exogenous dynamin (red) and acetylated tubulin (green). Note the accumulation of abundant acetylated tubulin in 551Δ3 expressing cells (middle). (from Tanabe & Takei, 2009)

Impaired dynamic instability of microtubules is known to inhibit intracellular trafficking along microtubules (Mimori-Kiyosue & Tsukita, 2003; Vaughan, 2005). Microtubule-dependent traffic can be analyzed by examining the formation of the Golgi apparatus because the biogenesis involves transport process of pre-Golgi compartment from cell periphery to perinuclear region, and this transport is dependent on microtubules (Thyberg & Moskalewski, 1999) (Fig.6).

While mature Golgi apparatus is ribbon-shaped localized at perinuclear region, immature pre-Golgi compartments are scattered throughout the cytoplasm. Golgi apparatus in the 551Δ3 expressing cells were massively fragmented, representing impaired microtubule-dependent vesicular traffic in the cells (Fig.7). This is consistent with impaired dynamic instability of microtubules in 551Δ3 expressing cells.

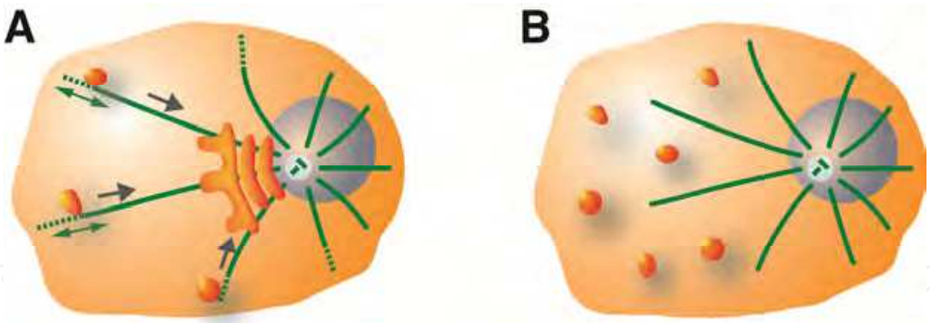

Fig. 6. Formation of mature Golgi apparatus by microtubule-dependent vesicular transport. Scheme showing radially arranged microtubules (green) and the formation of matured Golgi by microtubule dependent vesicular transport of immature pre-Golgi compartments (orange). Plus end of microtubules extends and shrinks dynamically and capture the cargo. (A). Loss of dynamic instability of microtubules impairs the microtubule-dependent transport.

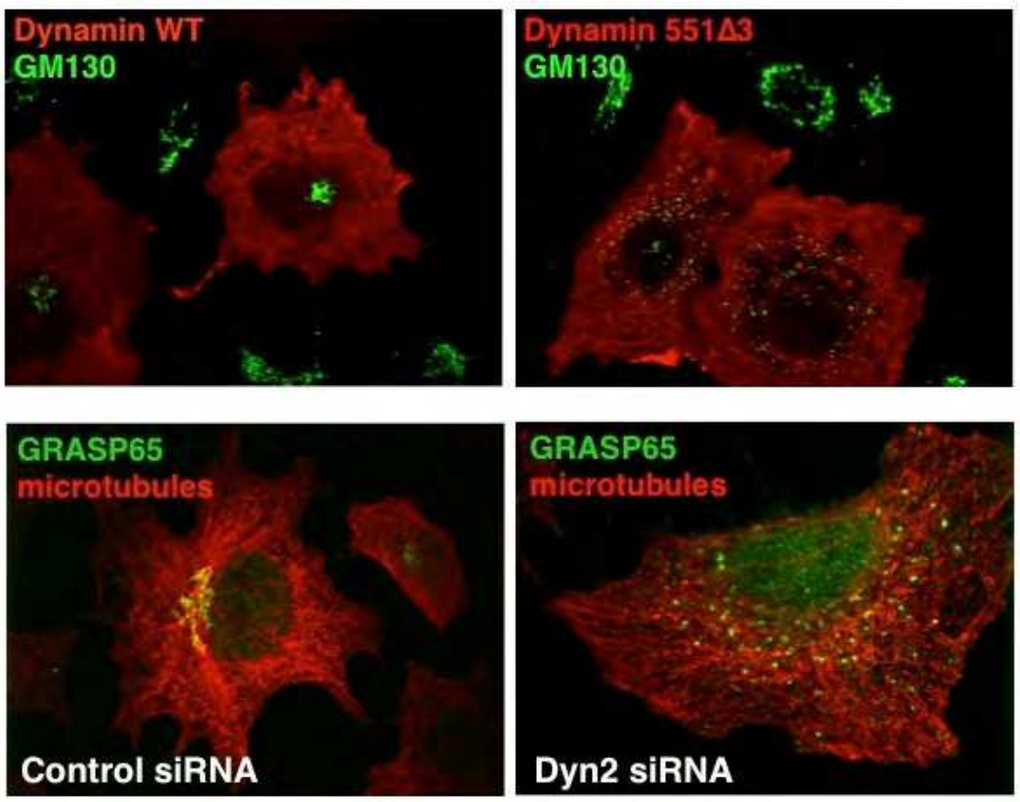

Fig. 7. Dynamin CMT mutant or dynamin 2 RNAi impairs the formation of Golgi apparatus. Upper panels: Expression of 551Δ3 dynamin 2 leads to Golgi fragmentation (right). COS-7 cells transfected with the indicated dynamin constructs were visualized by immunofluorescence for exogenous dynamin (red) and GM130, a Golgi marker (green). Lower panels: Dynamin 2 RNAi causes fragmentation of Golgi apparatus (right). HeLa cells were transfected with the indicated siRNAs and visualized with antibodies a Golgi marker GRASP65 (green) and α-tubulin (red). (from Tanabe & Takei, 2009)

4.2 Depletion of dynamin affects microtubule dynamics

Accumulation of acetylated microtubules and impairment of microtubule-dependent vesicular traffic induced by the 551Δ3 mutation are thought to be due to 'loss of function' of dynamin 2, because depletion of endogenous dynamin 2 in HeLa cells by RNAi resulted in similar phenotypes (Tanabe & Takei, 2009). Golgi apparatus was fragmented in approximately 90 % of dynamin 2 siRNA cells, indicating suppressed microtubule-dependent membrane transport. The dynamin 2 siRNA-treated cells did not show any apparent reorganization of microtubules by immunofluorescence. However, acetylated tubulin in the cells was increased approximately twofold while total tubulin protein level remain unchanged. In addition, EB1, which localizes at the plus-end of dynamic/growing microtubules, was significantly reduced in dynamin 2 siRNA cells, even though the EB1 expression levels were unaffected by the siRNA (Fig.8). This indicates that depletion of endogenous dynamin 2 reduces dynamic, growing microtubules.

5. Possible mechanism of the regulation of microtubule dynamics by dynamin

As described above, dynamin 2 is implicated in the dynamic instability of microtubules, and deletion or mutation of the protein impairs the microtubule dynamics. Then how dynamin regulates the microtubule dynamics?

Microtubule is regulated, both in polymerization and depolymerization, by many factors. While microtubule depolymerizing factors involve MCAK, a member of kinesin-13 family (Hunter ey al., 2003; Walczak, 2003), polymerization factors includes XMAP215, tau and doublecortin (Howard & Hyman, 2007; Kerssemakers et al., 2006). Furthermore, the microtubule plus-end proteins, including EB1, CLASPs and CLIP170, are also essential for dynamic instability of microtubules.

It would be possible that activity of these microtubule-regulating molecules is altered by the presence of dynamin on microtubules. In another words, microtubule-bound dynamin 2 might function as "ratchet" that limits the access of these molecules to microtubules. Physiologically, dynamin transiently interact with microtubules, resulting only small population of dynamin stays at "microtubule-bound" state. On the other hand, dynamin with CMT mutation has higher affinity to microtubules and preferably localizes at microtubules (Tanabe & Takei, 2009). This would lessen the access of microtubule-regulating molecules to microtubules, and as a result, causes to decrease polymerization-depolymerization cycle. It would be also possible that abundant presence of mutant dynamin on microtubules may mechanically obstruct polymerization and depolymerization of microtubules (Fig 9).

It is known that blocking interconversion between stable and dynamic microtubules using Taxol, a microtubule depolymerization inhibitor, results in abnormal rearrangement of microtubules (Green & Goldman, 1983). Consistently, abnormal accumulation of acetylated microtubules is observed in dynamin 551Δ3 expressing cells (Tanabe & Takei, 2009).

Live cell imaging of GFP tubulin stably expressed in HeLa cells revealed that dynamic instability of microtubules in dynamin 2-depleted cells was apparently decreased compared with control cells (Tanabe & Takei, 2009).

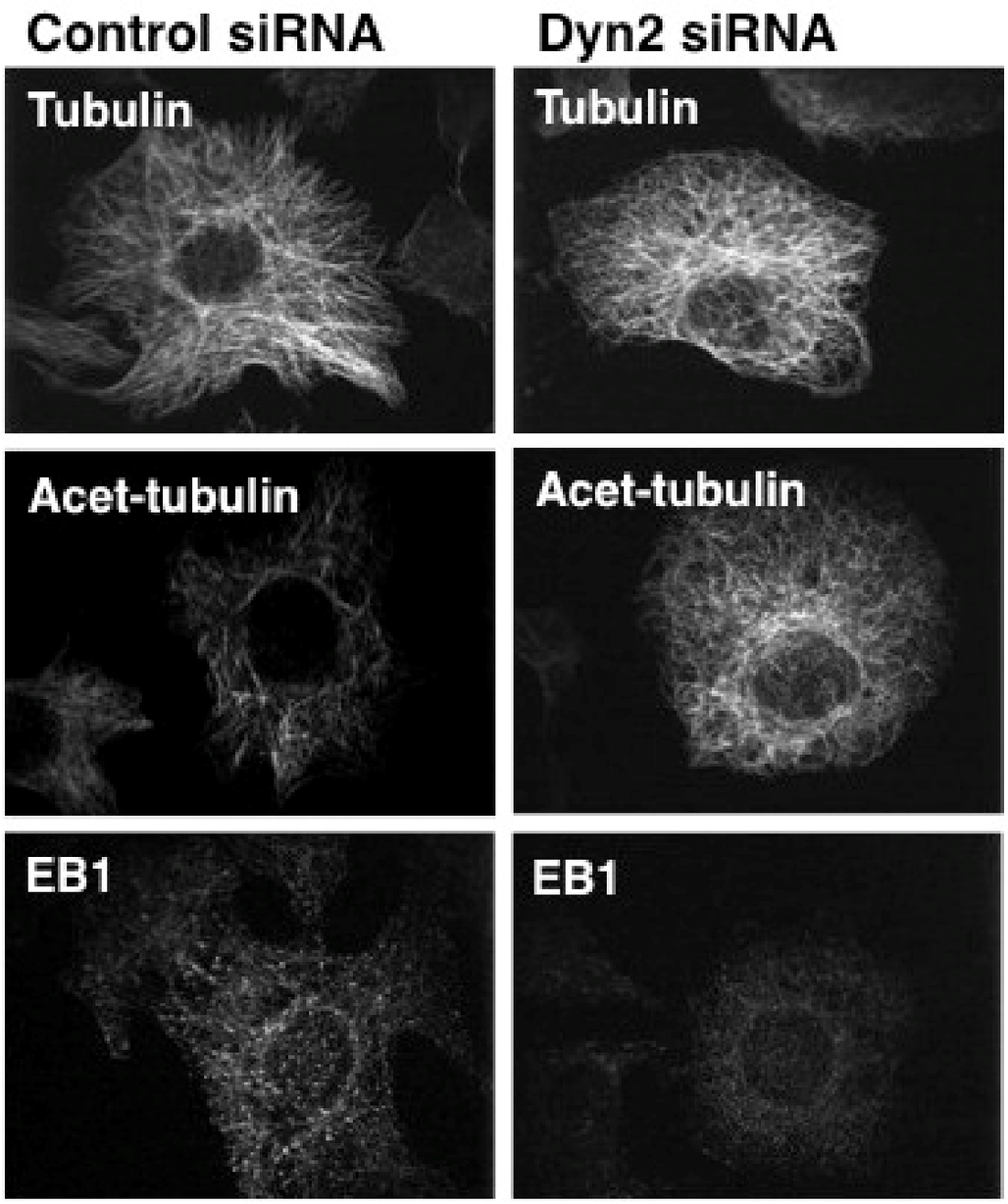

Fig. 8. Depletion of endogenous dynamin 2 by RNAi results in stable microtubule accumulation. HeLa cells cells transfected with control or dynamin 2 siRNA were stained by immunofluorescence as indicated. Note the increase of acetylated tubulin in dynamin 2 knocked-down cells (middle panels) while total tubulin is unchanged (top panels). In the knocked-down cells, punctate staining of EB1, microtubules plus end factor is lost (bottom panels). (from Tanabe & Takei, 2009)

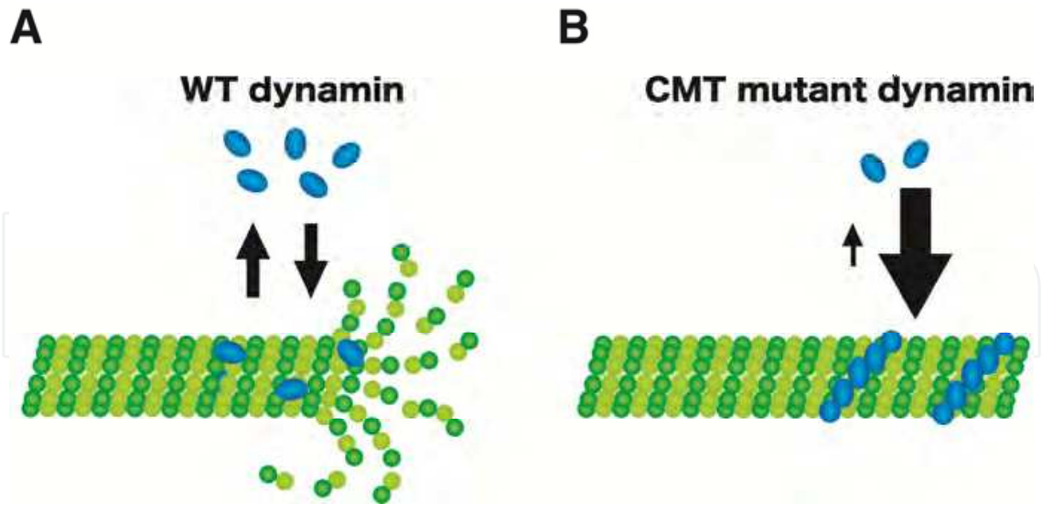

Fig. 9. Possible role of dynamin in the regulation of microtubule dynamics. Transient interaction of dynamin with microtubules would be essential for dynamic instability of microtubules (left). Mutation of dynamin would increase dynamin's affinity of to microtubules, which in turn obstructs polymerization-depolymerization cycle of microtubules either mechanically, or indirectly via microtubule-regulating molecules.

6. Conclusion

Dynamin has been originally identified as a microtubule-binding protein in 1989. However, the most of dynamin studies in the last two decades has been focused on its functions in endocytosis and actin dynamics. Our recent investigation on CMT mutant dynamin revealed impairment of microtubule dynamics and microtubule-dependent transport. Furthermore, this study led to the discovery of a novel role of dynamin, i.e. regulation of dynamic instability of microtubules.

It remains to be clarified which cells are more affected in the dynamin-caused CMT, in a correlation with clinical features of the disease. Since dynamin 2 is a ubiquitously expressed isoform, CMT mutations in dynamin 2 could affect either neurons, Schwan cells, or both. Precise molecular mechanism how dynamin regulates dynamic instability of microtubules would require future studies. Especially, it would be of importance which molecules function with dynamin in the microtubule regulation, or how dynamin-microtubule interaction is regulated.

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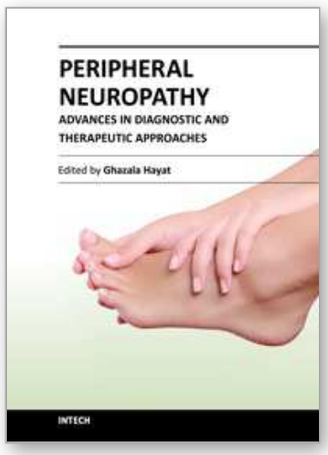

Peripheral Neuropathy - Advances in Diagnostic and Therapeutic Approaches

Edited by Dr. Ghazala Hayat

ISBN 978-953-51-0066-9
Hard cover, 206 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

Over the last two decades we have seen extensive progress within the practice of neurology. We have refined our understanding of the etiology and pathogenesis for both peripheral and central nervous system diseases, and developed new therapeutic approaches towards these diseases. Peripheral neuropathy is a common disorder seen by many specialists and can pose a diagnostic dilemma. Many etiologies, including drugs that are used to treat other diseases, can cause peripheral neuropathy. However, the most common cause is Diabetes Mellitus, a disease all physicians encounter. Disability due to peripheral neuropathy can be severe, as the patients suffer from symptoms daily. This book addresses the advances in the diagnosis and therapies of peripheral neuropathy over the last decade. The basics of different peripheral neuropathies is briefly discussed, however, the book focuses on topics that address new approaches to peripheral neuropathies.

How to reference

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Kohji Takei and Kenji Tanabe (2012). Etiological Role of Dynamin in Charcot-Marie-Tooth Disease, Peripheral Neuropathy - Advances in Diagnostic and Therapeutic Approaches, Dr. Ghazala Hayat (Ed.), ISBN: 978-953-51-0066-9, InTech, Available from: http://www.intechopen.com/books/peripheral-neuropathy-advances-in-diagnostic-and-therapeutic-approaches/etiological-role-of-dynamin-in-charcot-marie-tooth-disease

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