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Possible Diverse Roles of Fukutin: More Than Basement Membrane Formation?

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1. Introduction

Fukutin is a gene responsible for Fukuyama-type congenital muscular dystrophy (FCMD) (Kobayashi et al. 1998). FCMD is associated with ocular and central nervous system (CNS) malformation characterized by cobblestone lissencephaly (Fukuyama et al. 1960; Osawa et al. 1997), and is included in α -dystroglycanopathy, one of the groups of muscular dystrophy. α -dystroglycan (α -DG) is one of the components of dystrophin-glycoprotein complex (DGC) linking extracellular and intracellular proteins (Fig. 1). O-linked glycosylation is a characteristic of α -DG, which is necessary for binding of extracellular matrix proteins to form the basement membrane. Causative genes of α -dystroglycanopathy are related to the glycosylation of α -DG, and hypoglycosylation of α -DG is involved in the pathogenesis of α -dystroglycanopathy (Martin 2005; Michele & Campbell 2003; Schessl et al. 2006).

The pathomechanism of muscular, ocular and CNS lesions of FCMD has gradually been elucidated, and the sequence of the *fukutin* gene is also known [GenBank: AB008226] (Kobayashi et al. 1998). Like other α -dystroglycanopathy diseases, reduced glycosylation of α -DG is observed at the cellular/basement membrane of the striated muscle, eye and CNS of FCMD patients (Hayashi et al. 2001; Yamamoto et al. 2010). Although *fukutin* is related to the glycosylation of α -DG, its actual role in the glycosylation is unknown. Moreover, post-transcriptional regulation of *fukutin* still remains to be elucidated. Interestingly, besides basement membrane formation, *fukutin* seems to have additional functions.

2. Diseases included in α -dystroglycanopathy

FCMD, muscle-eye-brain disease (MEB), Walker-Warburg syndrome (WWS), and some other types of muscular dystrophies such as MDC (congenital muscular dystrophy) 1C, MDC1D, limb girdle muscular dystrophy (LGMD) 2I and LGMD2K are in the disease category of α -dystroglycanopathy. FCMD is a congenital disease characterized by muscular dystrophy associated with CNS and ocular lesions. It is the second most common muscular dystrophy in Japan and was first described in 1960 by Fukuyama et al. (Fukuyama et al. 1960). MEB was initially reported in Finland, and ocular anomalies are especially

conspicuous compared with FCMD (Pihko & Santavuori 1997). WWS is a severe disease and most of the patients die in infancy (Dobyns 1997). The CNS and eye are severely affected. The CNS lesions of FCMD, MEB and WWS are characterized by cobblestone lissencephaly, traditionally known as type II lissencephaly or polymicrogyria. Severe cases exhibit pachygyria. MDC1C (Brockington et al. 2001), MDC1D (Longman et al. 2003), LGMD2I (Brockington et al. 2001) and LGMD2K (Yis et al. 2011) are milder forms of α -dystroglycanopathy, in which CNS and eye lesions are less severe or absent. The clinical onset of LGMDs is late compared with that of congenital ones. Examples of animal models of α -dystroglycanopathy are fukutin chimeric mice (Chiyonobu et al. 2005; Masaki & Matsumura 2010), *large^{myd}* mice (Lee et al. 2005; Masaki & Matsumura 2010), *large^{vs}* mice (Lee et al. 2005; Masaki & Matsumura 2010), POMGnT1 knockout mice (Yang et al. 2007) and P0-DG null mice (Masaki & Matsumura 2010).

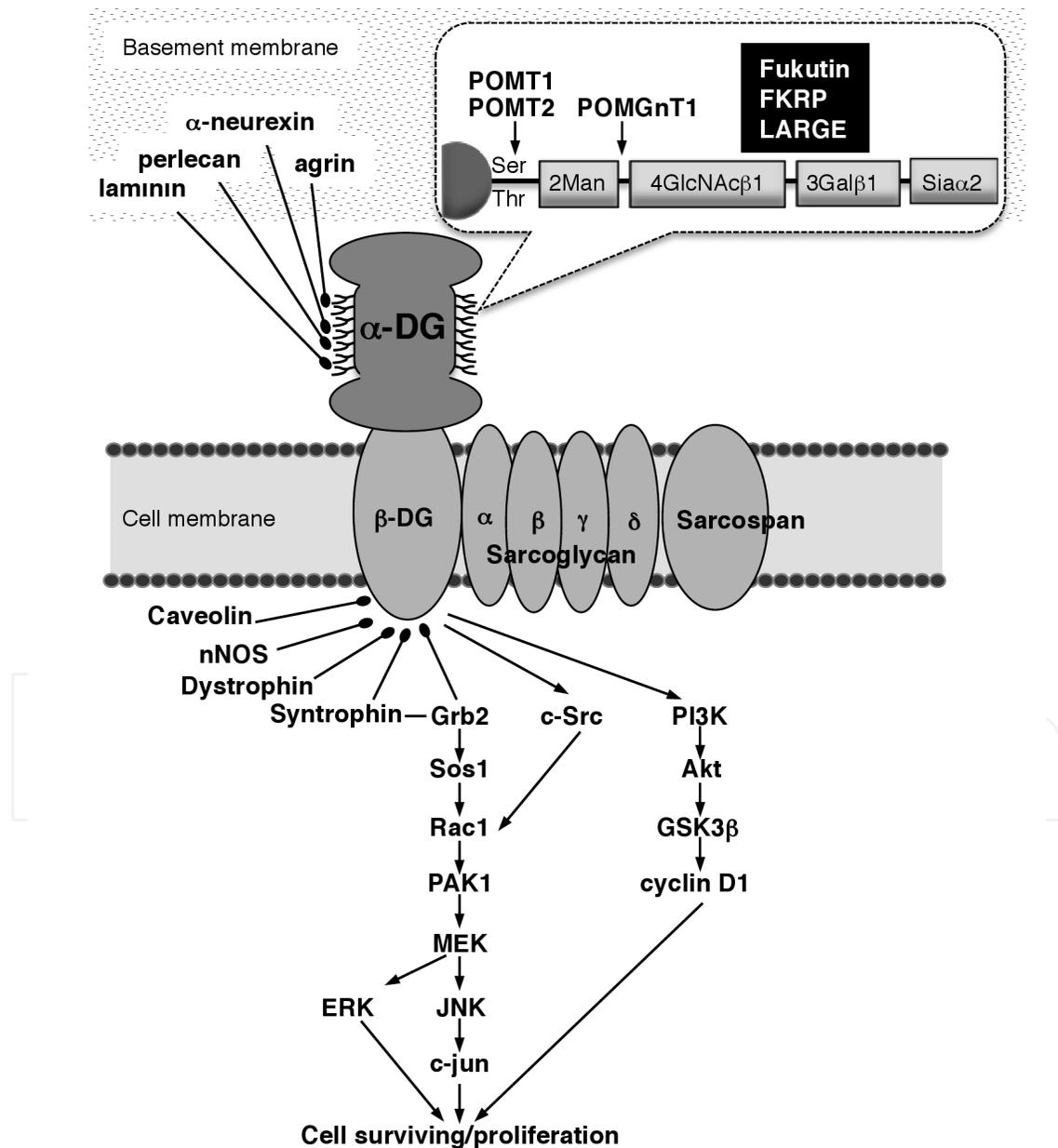


Fig. 1. A model of the dystrophin-glycoprotein complex in the skeletal muscle.

α -dystroglycanopathy shows the reduced glycosylation of α -DG at the cell/basement membrane. α -DG is a component of the DGC linking extracellular matrix and intracellular proteins (Fig. 1). It is a heavily glycosylated protein involved in the basement membrane formation by binding extracellular matrix proteins (Martin 2005; Michele & Campbell 2003; Schessl et al. 2006). Gene products involved in the glycosylation of α -DG include protein-*O*-mannosyltransferase 1 (POMT1), POMT2, *O*-linked mannosyltransferase β 1,2-*N*-acetylglucosaminyltransferase (POMGnT1), fukutin, fukutin-related protein (FKRP) and LARGE. α -dystroglycanopathy is caused by mutations of each gene. A wide spectrum of clinical disorders can be produced by mutations of one causative gene, especially *fukutin* and *FKRP* (Beltrán-Valero de Bernabé et al. 2003; Godfrey et al. 2007; Martin 2005; Schessl et al. 2006; Yis et al. 2011).

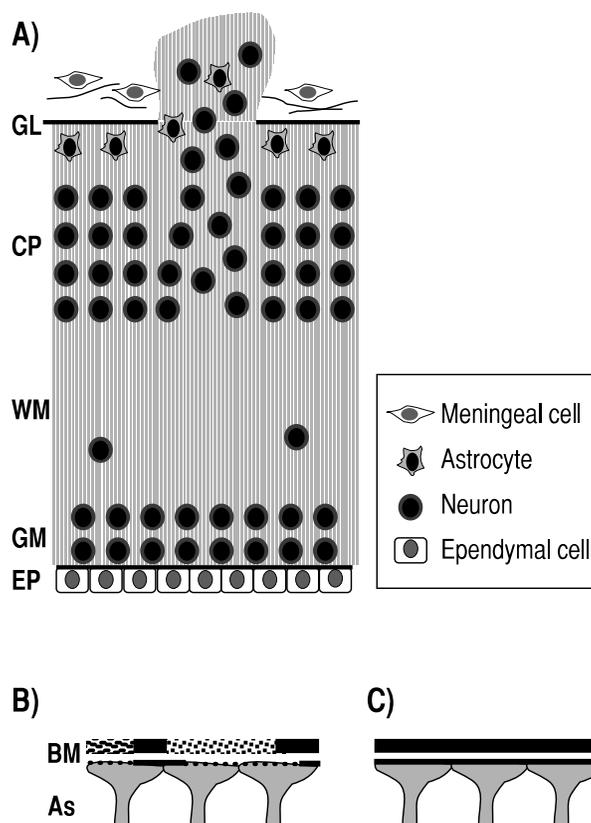
A common gene mutation of FCMD patients is homozygous founder mutation of *fukutin* (Kobayashi et al. 1998). However, a severe phenotype resembling WWS appears with heterozygous founder mutations and/or mutations that affect much of the coding protein (Beltrán-Valero de Bernabé et al. 2003; Cotarelo et al. 2008, Saito et al. 2000a), and milder phenotypes like LGMD have been reported (Godfrey et al. 2006; Godfrey et al. 2007; Murakami et al. 2006; Yis et al. 2011). *FKRP* mutations also produce clinical disorders over a wide spectrum covering most of the clinical phenotypes of α -dystroglycanopathy (Brockington et al. 2001; Martin 2005; Mercuri et al. 2006b; Schessl et al. 2006). *POMGnT1* is known as a gene responsible for MEB (Kano et al. 2002; Manyá et al. 2003; Yoshida et al. 2001), but WWS is also associated with mutations of *POMGnT1* (Martin 2005; Schessl et al. 2006; Taniguchi et al. 2003). Major genes responsible for WWS are *POMT1* (Akasaka-Manyá et al. 2004; Beltrán-Valero de Bernabé et al. 2002; Kim et al. 2004; Sabatelli et al. 2003) and *POMT2* (van Reeuwijk 2005), but milder phenotypes can occur as a result of their mutations (Balci et al. 2005; Biancheri et al. 2007; Mercuri et al. 2006a).

3. The glycosylation of α -DG for basement membrane formation, with regard to the pathogenesis of α -dystroglycanopathy

In striated muscle, glycosylated α -DG binds to several extracellular matrix proteins, such as laminin, agrin and neuroligin, to form the basement membrane (Fig. 1) (Masaki & Matsumura 2010; Michele and Campbell 2003). After translation, DG is cleaved into α - and β -DG (Ibraghimov-Beskrovnyaya et al. 1992; Michele and Campbell 2003). The C-terminal region of α -DG binds to the N-terminus of β -DG, a transmembrane protein. α -DG undergoes *N*-linked and *O*-linked glycosylation, and Sia- α -2,3-Gal- β -1,4-GlcNAc- β -1,2-Man-Ser/Thr in the mucin-like domain is involved in the interaction with laminin (Masaki & Matsumura 2010; Michele and Campbell 2003; Yoshida-Moriguchi et al. 2010). POMT1 together with POMT2 is required for the addition of mannose to a Ser/Thr residue (Manyá et al. 2004), and POMGnT1 for the next step (Takahashi et al. 2001). These proteins possess glycosyltransferase activities (Manyá et al. 2004; Takahashi et al. 2001). Although fukutin, FKRP and LARGE are related to the glycosylation of α -DG, it has not been fully elucidated how they work during the α -DG glycosylation (Martin 2005; Schessl et al. 2006). Recently, it has been clarified that phosphorylation on the *O*-linked mannose is required of α -DG for laminin binding, and this modification is mediated by LARGE (Yoshida-Moriguchi et al. 2010).

In α -dystroglycanopathy, epitopes recognized by monoclonal antibodies, IIIH6 and VIA4-1 (Ervasti & Campbell 1993; Martin 2005; Michele and Campbell 2003), are reduced in the sarcolemma of the striated muscle, immunohistochemically. In western blotting, the hypoglycosylation is exhibited by a reduction of the molecular weight: a band of about 156 kDa in normal skeletal muscles shifts to a lower weight in muscles in cases of α -dystroglycanopathy. This hypoglycosylation is considered to cause a loss of α -DG function as a receptor for extracellular matrix proteins, which results in muscular dystrophy.

DGC similar to that of the skeletal muscle is observed in the peripheral and central nervous systems. In the CNS, the glia limitans is covered with the basement membrane where the glycosylated α -DG is observed. Morphological abnormalities of the basement membrane and the glia limitans have been reported in the CNS of FCMD (Fig. 2) (Nakano et al. 1996; Takada et al. 1987; Yamamoto et al. 1997; Yamamoto et al. 2010) and WWS (Beltrán-Valero de Bernabé 2002; Miller et al. 1991) patients and in mouse models of FCMD (Chiyonobu et al. 2005) and MEB (Yang et al. 2007). Fragile basement membrane caused by hypoglycosylation



GL: glia limitans, CP: cortical plate, WM: white matter, GM: germinal matrix, EP: ependymal cells, BM: basement membrane, As: endfeet of astrocytes

Fig. 2. Schemas of the glia limitans of fetal FCMD cerebrum. A) Immature neurons and glia over-migrate into the leptomeninges through disruption of the glia limitans. B) The glia limitans is composed of astrocytic endfeet covered with the basement membrane. In the glia limitans of FCMD, both cell and basement membranes of astrocytes become ambiguous, even in the area without disruption, electron microscopically. Distribution of the abnormality is irregular. C) The cell and basement membranes are linear in controls.

of α -DG induces disruption of the glia limitans in the fetal period, which is considered to result in cobblestone lissencephaly. The glia limitans is formed by endfeet of astrocytes, and reduction of laminin binding has been observed in an astrocytoma cell line by knockdown of fukutin (data not shown). Astrocytes are considered to play an important role in the pathogenesis of the CNS lesion of α -dystroglycanopathy.

Thus, hypoglycosylation of α -DG at the basement membrane is involved in the pathogenesis of α -dystroglycanopathy. However, a wide clinical spectrum of disorders due to mutations of each causative gene might not be explained only by the abnormal basement membrane (Jiménez-Mallebrera et al. 2009).

4. Clinicopathological characteristics of FCMD

Generally, FCMD patients are found as a floppy infant, achieve peak motor function between 2 and 8 years, and die before 30 years old. They are mentally retarded, and more than 50% of patients have seizure. Abnormal eye movement and myopia are frequently seen, and cardiac symptoms may also be present (Fukuyama et al. 1960; Osawa et al. 1997). However, clinical manifestations of FCMD vary widely from mild to severe: patients of mild type can walk and talk meaningfully to some extent, while severe ones are very retarded and some cases may die *in utero*.

In the skeletal muscle, muscle fibers markedly decrease in number, which is associated with interstitial fibrosis and fatty infiltration. Myocardial fibrosis of varying degrees is observed in patients, particularly those more than 10 years old (Osawa et al. 1997). In eyes, retinal dysplasia with discontinuity of the inner limiting membrane is observed (Hino et al. 2001). In the cobblestone lissencephaly of post-natal patients, disorganization of cortical neurons, heterotopic glioneuronal tissues and surface fusions are seen, histologically (Kamoshita et al. 1976; Takada et al. 1984). Generally, the cerebral cortical lesion is extensive, but the cerebellum and brainstem are partially or mildly affected. Pachygyria and migration arrest are clear in severe cases mimicking WWS. On the other hand, a portion of the cerebral cortex shows an almost normal-looking appearance in mild cases. In fetal cases, the glia limitans formed by astrocytic endfeet in the CNS surface is disrupted, through which the glioneuronal tissues over-migrate into the leptomeninges (Fig. 2) (Nakano et al. 1996; Takada et al. 1987; Yamamoto et al. 1997; Yamamoto et al. 2010). Even in non-disrupted areas, both cell and basement membranes are abnormal, electron microscopically (Yamamoto et al. 1997; Yamamoto et al. 2010). The degree of disruption varies from case to case and even from area to area in a single patient (Takada et al. 1987; Yamamoto et al. 1997).

5. Functions of fukutin

5.1 *Fukutin* gene

Fukutin gene [GenBank, Accession AB038490] spans more than 100 kb of genomic DNA on chromosome 9q31 (Kobayashi et al. 1998; Toda et al. 1994). *Fukutin* mRNA composed of 10 exons is 7,349 bp with an open reading frame of 1,383 bp, beginning at base 112 (Kobayashi et al. 1998). *Fukutin* protein has 461 amino acids and the calculated molecular weight is 53.6 kDa, containing a hydrophobic signal sequence in the N-terminal (Kobayashi et al. 1998).

Retrotransposal 3-kb insertion of tandemly repeated sequences in the 3'-untranslated region is a common gene abnormality in FCMD patients and was determined as the ancestral founder haplotype (Kobayashi et al. 1998). Other mutations such as missense and nonsense mutations have been found (Beltrán-Valero de Bernabé 2003; Kobayashi et al. 1998). Japanese FCMD patients carry at least one copy of a founder mutation (Yoshioka 2009).

5.2 Functions of fukutin besides basement membrane formation in the nervous system

Fukutin is involved in basement membrane formation via the glycosylation of α -DG as described above. From the standpoint of CNS malformation, the most important component in the CNS is astrocytes that form the glia limitans. However, from the standpoint of total CNS function, the roles of fukutin in other components should be kept in mind during and after development (Fig. 3).

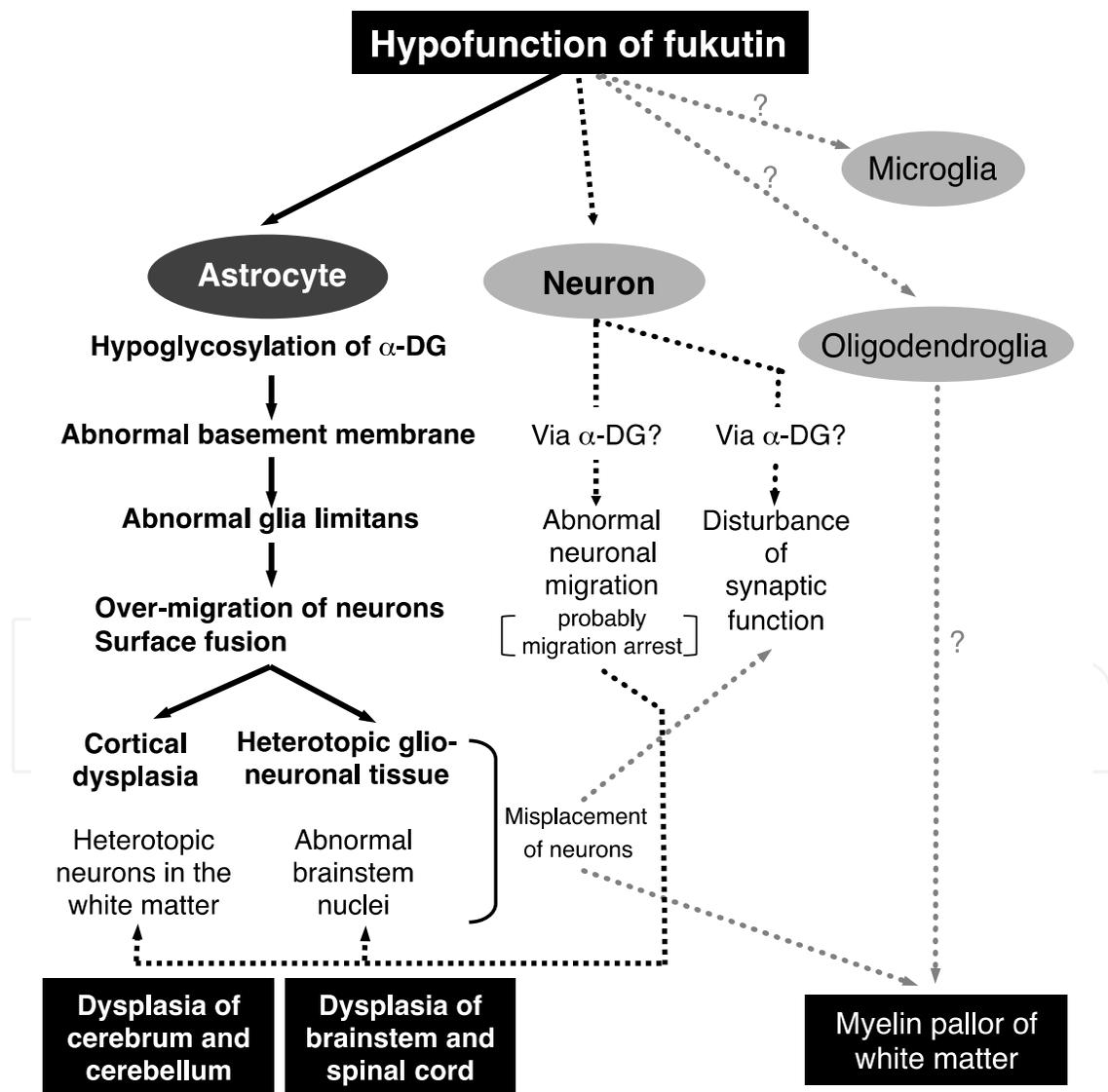


Fig. 3. Hypothesis for the CNS lesion of FCMD.

Fukutin is expressed in mature and immature neurons (Saito et al. 2000b; Sasaki et al. 2000; Yamamoto et al. 2002; Yamamoto et al. 2010). Mature neurons express α -DG detected by the antibody of VIA4-1, but not IHH6C4 (Hayashi et al. 2001; Hiroi et al. 2011; Saito et al. 2006). α -DG is considered to be involved in post-synaptic function (Moore et al. 2002; Satz et al. 2010). Since fukutin and the glycosylated α -DG are co-expressed in mature neurons, fukutin may be involved in synaptic function via the glycosylation of α -DG (Hiroi et al. 2011; Saito et al. 2006).

In the fetal cerebral and cerebellar cortex, fukutin and the glycosylated α -DG detected by VIA4-1 are co-expressed in immature neurons, especially in cells before and during migration (Hiroi et al. 2011). Fukutin may be involved in neuronal migration via the glycosylation of α -DG. However, this function appears to be minimal or immediately compensated for by other molecules because migration arrest in the FCMD brain is slight (Saito et al. 2003; Yamamoto et al. 2010), and forebrain histogenesis is preserved in mice with a neuron-specific deletion of DG (Satz et al. 2010).

The expression and function of fukutin in oligodendroglia and microglia are unclear. However, in the peripheral nerve, the DGC is found in Schwann cells, a counterpart of oligodendroglia, and is related to myelination and myelin maintenance (Masaki and Matsumura 2010). Fukutin-deficient chimeric mice exhibit a loss of myelination in the peripheral nerve (Masaki and Matsumura 2010; Saito et al. 2007), so that a function of oligodendroglia may be impaired.

Thus, fukutin is considered to have functions in neurons and glia, presumably mediated by the glycosylation of α -DG, which are not restricted to basement membrane formation. Interestingly, since neither mature nor immature neurons are positive for IHH6C4, the glycosylation of α -DG may be different between astrocytes and neurons (Hiroi et al. 2011). An experiment using mice genetically treated to lose DG in various patterns demonstrated a difference between glial and neuronal DG (Satz et al. 2010). Difference in DG glycosylation in different types of cells may be one of the reasons for the broad spectrum of CNS lesions of cobblestone lissencephaly (Satz et al. 2010).

5.3 Possible involvement of fukutin in neuroglial differentiation

The adult human cerebrum and cerebellum show less expression of fukutin than fetal ones, on immunohistochemistry and *in situ* hybridization (Saito et al. 2000b; Yamamoto et al. 2002). Fukutin expression is reduced after differentiation of cultured neuronal cells (Hiroi et al. 2011). Neuroblastoma cells extend neurites after knockdown of fukutin by RNAi (Fig. 4) (Hiroi et al. 2011). In an astrocytoma cell line, cells elongate cytoplasmic processes with increased expression of glial fibrillary acidic protein after knockdown of fukutin, and cells become epithelioid with an increase of Musashi-1 protein by transfection of fukutin (data not shown). Fukutin may be involved in neuroglial differentiation. In neurons, fukutin appears to prevent neuronal differentiation during migration. Although it is not clear whether this process is mediated by the glycosylation of α -DG, this seems very reasonable because immature neurons begin to differentiate after settlement in an appropriate site of the cortex.

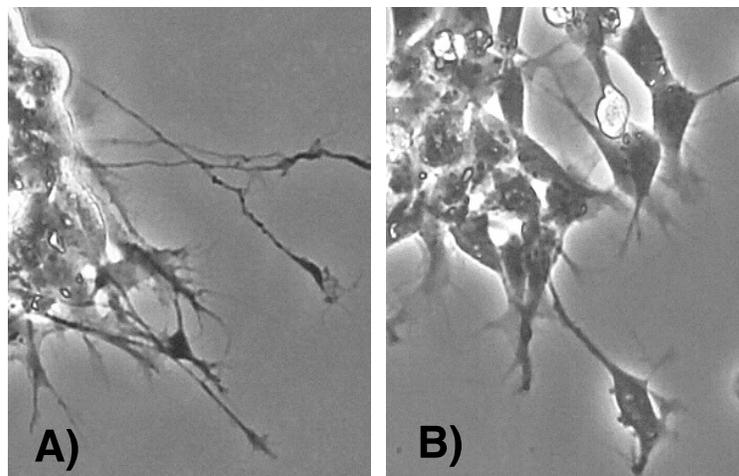


Fig. 4. RNAi in neuroblastoma cell line, IMR-32. After knockdown of fukutin, cells elongate neurites more (A) than in a control (B).

5.4 Functions of fukutin in somatic cells

Fukutin is expressed in various somatic organs (Kobayashi et al. 1998; Yamamoto et al. 2010). The DGC exists in epithelial cells, and DG plays a role in regulating cytoskeletal organization, cell polarization and cell growth in epithelial cells (Sgambato & Brancaccio 2005). Decrease of glycosylated α -DG has been reported in various cancers, and DG may act as a cancer suppressor (Sgambato & Brancaccio 2005). In a human non-tumorigenic mammary cell line, the percentage of cells in G_0/G_1 phase of the cell cycle is increased by DG overexpression (Sgambato et al. 2004). Since the DGC is linked to the cell signaling pathway (Oak et al. 2003) the glycosylation of α -DG can influence cell proliferation. At the C-terminus, β -DG binds to dystrophin and other intracellular proteins connecting to cell signaling pathways, such as growth factor receptor bound protein 2 (Grb2) involved in the MAPK/ERK cascade (Fig. 1) (Oak et al. 2003; Masaki and Matsumura 2010), with c-jun in the downstream region of the pathway (Oak et al. 2003). Tyrosine phosphorylation of the C-terminus of β -DG is dependent on c-src (Oak et al. 2003, Sotiga et al. 2001), and a signaling pathway is activated by laminin binding initiated by src family kinase (Zhou et al. 2007). The PI3K/AKT pathway is also involved (Langenbach et al. 2002).

Participating in the glycosylation of α -DG in epithelial cells as well (Yamamoto et al. 2008), fukutin may affect various epithelial cellular functions via the glycosylated α -DG. Fukutin may suppress cell proliferation/survival in epithelial cells because knockdown of fukutin in cancer cell lines made them proliferate more, at least in the short term (Yamamoto et al. 2008). There is a possibility of unknown functions of fukutin without intervention of the glycosylation of α -DG because nuclear localization of fukutin is suggested in cancer cell lines (Yamamoto et al. 2008). Involvement of fukutin in an immunological system is also supposed because fukutin is expressed in lymphoblast (Kobayashi et al. 1998).

The effects of fukutin might be different in different kinds of cells since cellular proliferation showed no change or rather a reduction after knockdown of fukutin in astrocytoma cells (data not shown). More experiments are required to clarify this point because there might have been some technical problems and alternative splicing has been reported in fukutin (Kobayashi et al. 2001).

5.5 Characteristics of fukutin mRNA with regard to neuroglial functions

In the CNS, synaptic plasticity is an important mechanism to adapt neurons to varying circumstances. Quick responses are needed at dendrites. Plasticity may also be required in astrocytes. Astrocytic endfeet are components of the blood-brain barrier (BBB), which maintains the CNS function by regulating transportation of water and various molecules. In the BBB, the basement membrane, positive for antibodies against glycosylated α -DG, VIA4-1 and IHH6C4, is formed between capillary and astrocytic endfeet. Moreover, the glycosylated α -DG is a receptor for some microorganisms (Cao et al. 1998; Kunz et al. 2005; Masaki and Matsumura 2010; Rambukkana et al. 1998). The glycosylation of α -DG should be prompt to adapt to varying circumstances at the most peripheral part of a cell.

There is a special type of mRNA called localized mRNA that is related to the maintenance of cell polarity, asymmetrical segregation and synaptic plasticity (López de Heredia and Jansen 2004; Ule and Darnell 2006). Localized mRNA has a binding site of an RNA-binding protein in the 3'-UTR region. A complex composed of mRNA and proteins is transported to peripheral areas of a cell such as dendrites, using a molecular motor like dynein and kinesin (López de Heredia and Jansen 2004). After reaching an appropriate site, the mRNA starts to be translated. mRNA of *Arc*, the immediate early gene product related to synaptic plasticity, is one of the localized mRNAs. A complex consisting of *Arc* mRNA and several proteins is transported along the microtubules and the mRNA undergoes local translation at a site of synaptic activity (Bramham et al. 2010). Kinesin is a motor of this complex. The transcription of *Arc* is regulated by cyclic AMP response element binding protein (CREB) (Bramham et al. 2010). A CRE-like sequence has been found in the fukutin gene promoter, and the transcription of fukutin may be regulated by CREB (Fang et al. 2005). Taking account of the possible functions of fukutin at the synapse and the BBB, it seems reasonable that fukutin mRNA is a localized mRNA. In the experiment using an astrocytoma cell line, Musashi-1 protein, one of the RNA-binding proteins, may bind to the 3'-UTR region of fukutin mRNA, suggesting that fukutin is a localized mRNA (data not shown).

6. Therapeutic strategies

From a therapeutic standpoint, many new strategies are underway for muscular dystrophy, particularly Duchenne muscular dystrophy (Collins & Bönnemann 2010; Cossu & Sampaolesi 2007; Muntoni et al. 2007; Odom et al. 2007). For α -dystroglycanopathy, full restoration of α -DG glycosylation might not be required (Kanagawa et al. 2009). Gene delivery using adeno-associated virus vectors may be applicable because causative genes of α -dystroglycanopathy are small enough to be packaged into this vector (Collins & Bönnemann 2010; Odom et al. 2007). Gene therapy using *LARGE* may be one of the candidates because gene transfer of *LARGE* restores α -DG receptor function not only in *Large^{myd}* mice but also in cultured cells from FCMD, MEB and WWS patients (Barresi et al. 2009). Transgenic overexpression of T-cell GalNAc transferase (*GALgt2*) in the skeletal muscle increases glycosylation of α -DG (Collins & Bönnemann 2010; Yoon et al. 2009). Transfer of *fukutin* restores glycosylation of α -DG in knock-in mice carrying the retrotransposal insertion in the mouse *fukutin* ortholog (Kanagawa et al. 2009).

However, there is a big underlying problem in patients with CNS malformation. Strategies might have to be different between muscle and CNS. The complicated structure of the CNS

composed of several components should be noted. On FCMD, fukutin is expressed at least in astrocytes and neurons in the CNS. If the functions of fukutin in these cells are compensated for by other molecules after development, a therapy during the critical period *in utero* might be sufficient. In contrast, if fukutin continues to play important roles after development, lifelong therapy should be applied. In terms of future advances and applications of gene therapy for FCMD, it may be necessary to determine its precise roles to achieve an effective method while avoiding unprecedented side effects as much as possible. Since fukutin has several isoforms derived from alternative splicing (Kobayashi et al. 2001), investigations of each isoform may also be required.

7. Conclusion

Fukutin is related to the glycosylation of α -DG, which is involved in the pathogenesis of muscular dystrophy and ocular and CNS malformation of FCMD. Besides the basement membrane formation, fukutin has more diverse roles in other cells, including synaptic function and neuronal migration. Determination of the precise roles of fukutin seems to be important for further understanding of the disease and for future gene therapy.

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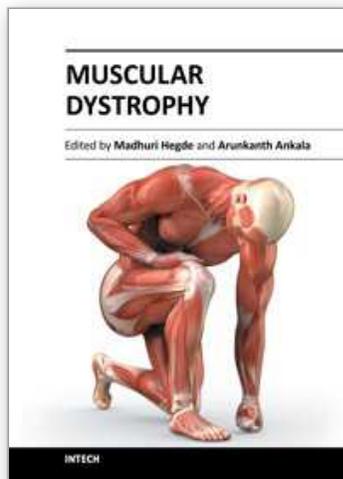
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With more than 30 different types and subtypes known and many more yet to be classified and characterized, muscular dystrophy is a highly heterogeneous group of inherited neuromuscular disorders. This book provides a comprehensive overview of the various types of muscular dystrophies, genes associated with each subtype, disease diagnosis, management as well as available treatment options. Though each different type and subtype of muscular dystrophy is associated with a different causative gene, the majority of them have overlapping clinical presentations, making molecular diagnosis inevitable for both disease diagnosis as well as patient management. This book discusses the currently available diagnostic approaches that have revolutionized clinical research. Pathophysiology of the different muscular dystrophies, multifaceted functions of the involved genes as well as efforts towards diagnosis and effective patient management, are also discussed. Adding value to the book are the included reports on ongoing studies that show a promise for future therapeutic strategies.

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