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Review

# Mechanistic aspects of the formation of α-dystroglycan and therapeutic research for the treatment of α-dystroglycanopathy: A review

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ABSTRACT

α-Dystroglycanopathy, an autosomal recessive disease, is associated with the development of a variety of diseases, including muscular dystrophy. In humans, α-dystroglycanopathy includes various types of congenital muscular dystrophy such as Fukuyama type congenital muscular dystrophy (FCMD), muscle eye brain disease (MEB), and the Walker Warburg syndrome (WWS), and types of limb girdle muscular dystrophy 2I (LGMD2I). α-Dystroglycanopathy share a common etiology, since it is invariably caused by gene mutations that are associated with the *O*-mannose glycosylation pathway of α-dystroglycan (α-DG). α-DG is a central member of the dystrophin glycoprotein complex (DGC) family in peripheral membranes, and the proper glycosylation of α-DG is essential for it to bind to extracellular matrix proteins, such as laminin, to cell components. The disruption of this ligand-binding is thought to result in damage to cell membrane integration, leading to the development of muscular dystrophy. Clinical manifestations of α-dystroglycanopathy frequently include mild to severe alterations in the central nervous system and optical manifestations in addition to muscular dystrophy. Eighteen causative genes for α-dystroglycanopathy have been identified to date, and it is likely that more will be reported in the near future. These findings have stimulated extensive and energetic investigations in this research field, and novel glycosylation pathways have been implicated in the process. At the same time, the use of gene therapy, antisense therapy, and enzymatic supplementation have been evaluated as therapeutic possibilities for some types of α-dystroglycanopathy. Here we review the molecular and clinical findings associated with α-dystroglycanopathy and the development of therapeutic approaches, by comparing the approaches with the development of Duchenne muscular dystrophy.





*Abbreviations:* α-DG, alpha-dystroglycan; FCMD, Fukuyama type congenital muscular dystrophy; MEB, muscle eye brain disease; WWS, Walker Warburg syndrome; LGMD2I, limb girdle muscular dystrophy 2I; DGC, dystrophin glycoprotein complex; DMD/BMD, Duchenne muscular dystrophy/Becker muscular dystrophy; LG, laminin globular; Rbo5P, ribitol 5-phosphate; ISPD, isoprenoid synthase domain-containing; MDDG, muscular dystrophy-dystroglycanopathy; CDPRbo, cytidine diphosphate ribitol; CGD, congenital disorders of glycosylation; NMJ, neuromuscular junction; AAV9, adeno-associated virus 9.

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## 1. Introduction

Muscular dystrophy is a clinically and genetically heterogeneous group of diseases that cause progressive weakness of the skeletal muscle and a gradual loss of motor function. The number of genes associated with the development of muscular dystrophies has been expanding quite recently due to progress in the area of molecular technology, and the various categories of muscular dystrophies have also been rearranged in a more reasonable manner (Mercuri and Muntoni, 2013). More than 30 diseases are currently categorized as constituting muscular dystrophy, and more than 50 genes have been identified as causative factors for these muscular dystrophies (Mercuri and Muntoni, 2013).

The most well-known muscular dystrophy is X-linked type Duchenne muscular dystrophy/Becker muscular dystrophy (DMD/BMD). The causative gene, *dystrophin*, was identified in 1987 (Koenig et al., 1987). After 30 years, extensive advances in basic research directed at DMD have led to the launching of several clinical trials (Leung and Wagner, 2013). On the other hand, α-dystroglycanopathy is a newly emerging subcategory among muscular dystrophies, and is characterized by systemic manifestations such as in the brain and eye anomalies, similar to muscular dystrophy. α-Dystroglycan (α-DG) was identified in 1990 as a glycoprotein that is located on the peripheral membrane in muscle tissue (Ervasti et al., 1990; Ibraghimov-Beskrovnaya et al., 1992). A defect in the glycosylation of α-DG was identified in skeletal muscle of the patients with Fukuyama type congenital muscular dystrophy (FCMD), thus confirming the existence of α-dystroglycanopathy (Hayashi et al., 2001). Since then, a deficiency in the glycosylation of α-DG was also reported in muscle tissue with muscle eye brain disease (MEB), the Walker Warburg syndrome (WWS) (Michele et al., 2002), limb girdle type muscular dystrophy patients with mutations in the fukutin related protein (*FKRP*) (Brockington et al., 2001), and with like-acetylglucosaminyltransferase (*LARGE*) mutations (Longman et al., 2003). Fukuyama et al. (1981) reported FCMD as a new disease category of congenital muscular dystrophy with a brain anomaly in 1960. Indeed, the term, "α-dystroglycanopathy" emerged more than 40 years later, and these diseases are now recognized as forms of muscular dystrophy commonly characterized by the incomplete glycosylation of α-DG (Michele and Campbell, 2003; Toda et al., 2003).

Clinically, α-dystroglycanopathy was originally classified as a severe type of congenital muscular dystrophy with eye and brain anomalies, but gradually, a wide range of phenotypes, such as milder symptoms without mental retardation or eye anomalies, have been reported (D'Amico et al., 2006; Murakami et al., 2006). There are now a wide variety of phenotypic and genotypic varieties in this category and the classification has become quite complicated. Recently, a simplified category for α-dystroglycanopathy, based on phenotype and genotype, has been proposed (Godfrey et al., 2011). As these precise clinical and molecular characterizations of α-dystroglycanopathy have progressed, several successful basic research targeting molecular therapies in this field such as gene therapy, antisense therapy, and enzyme replacement therapy have emerged. In this review, we summarize the extensive progress in clinical characterization and basic research in α-dystroglycanopathy and recent progress in developing therapeutic approaches for the treatment of α-dystroglycanopathy.

## 2. α-Dystroglycanopathy

### 2.1. Molecular findings of α-dystroglycanopathy

Dystroglycan (DG) was isolated from skeletal muscle as a component of the dystrophin-glycoprotein complex (DGC) on the peripheral membrane (Ervasti et al., 1990). Since genetic defects in most of these DGC components, such as dystrophin, sarcoglycan, caveolin, and syntrophins, cause muscular dystrophy, DGC is a central component in maintaining muscle membrane stability (Cohn and Campbell, 2000; Nowak and Davies, 2004; Ozawa et al., 1995). DG is composed of two subunits (alpha and beta), and it is encoded by a single gene (*DAG1*) on chromosome 3p21, and cleaved into α-DG and β-DG during posttranslational processing (Ibraghimov-Beskrovnaya et al., 1992). α-DG on the peripheral membrane binds to β-DG, a transmembrane intracellular glycoprotein. β-DG binds to dystrophin, which is connected to the actin cytoskeleton.

α-DG functions as a ligand for molecules associated with the extracellular matrix such as laminin (Ervasti and Campbell, 1993), perlecan (Talts et al., 1999), agrin (Bowe et al., 1994), neurexin (Sugita et al., 2001), pikachurin (Sato et al., 2008), and slit (Wright et al., 2012) via heavily glycosylated *O*-mannose (*O*-Man) type sugar moieties. Thus the physical link between the extracellular matrix and the

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