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Review Article

The Roles of A-Dystroglycan in the Central Nervous System-

Man Qi Li¹ and Yi Luo^{2*}

¹Department of Foreign Language, Yangtze University College of Arts and Science, Jingzhou 434000, China

²Department of Neurology, The First People's Hospital of Jingzhou, the First Affiliated Hospital of Yangtze University, Jingzhou 434000, China

***Address for Correspondence:** Yi Luo, Department of Neurology, The First People's Hospital of Jingzhou, the First Affiliated Hospital of Yangtze University, Jingzhou 434000, China,
E-mail: luoyitj@126.com / 454390553@qq.com

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ABSTRACT

Dystroglycan is a membrane protein, which is related to extracellular matrix in various mammalian tissues. α -subunit of Dystroglycan (α -DG) is highly glycosylated, including a special O-mannose group, depending on this unique glycosylation to bind its ligands. Different groups of muscular dystrophies are caused by a low glycosylation of α -DG, accompanied by the involvement of the central nervous system, from the brain malformation to intellectual retardation. More and more literatures discuss α -DG in the central nervous system, from the brain development to the maintenance of synapses. The goal of this review is to synthesize the information from these literatures, formulating an up-to-date understanding of various functions about α -DG in central nervous system. Where possible, we combine these data with our knowledge to promote translation from the perspective of basic medicine to clinical treatment.

INTRODUCTION

In the tissues of multicellular living beings, different cell types establish the molecular connections between cells and extracellular substrates. Therefore, the Extracellular Matrix (ECM) and cell surface adhesion complex establish connections to support the functional morphology and physiology of different tissues during the development. A series of ECM proteases, cell adhesion receptors and ECM proteins have been identified in animals and human beings [1,2]. Above them, Dystroglycan (DG) plays an important role in the formation of molecular contact to stabilize the connections between cells (Figure1) [3].

DG is encoded by a single gene (DAG1) on chromosome 3p21, and cleaved into α -DG and β -DG during posttranslational processing [4]. α -DG was confirmed as a glycoprotein in 1990 that is located on the peripheral membrane of muscle tissue [5]. α -DG on the peripheral membrane binds to β -DG. β -DG binds to dystrophin, which is connected to the actin cytoskeleton (Figure1) [6,7]. A defect in glycosylation of α -DG was discovered in skeletal muscle of the patients with Fukuyama Type Congenital Muscular Dystrophy (FCMD) to confirm the presence of α -dystroglycanopathy [8]. In addition, the deficiency of α -DG glycosylation was also identified in limb girdle type muscular dystrophy patients with mutations in the Fukutin Related Protein (FKRP) [9] and with Like-Acetylglucosaminyltransferase (LARGE) mutations, the Walker Warburg Syndrome (WWS) with Muscle Eye Brain Disease (MEB) [10]. Beside from skeletal muscle, α -DG is also found in cells of nervous system, digestive tract, kidney, skin and reproductive organs [7,11-14]. Many functions have been ascribed to α -DG, depending on the developmental and cell-specific contexts.

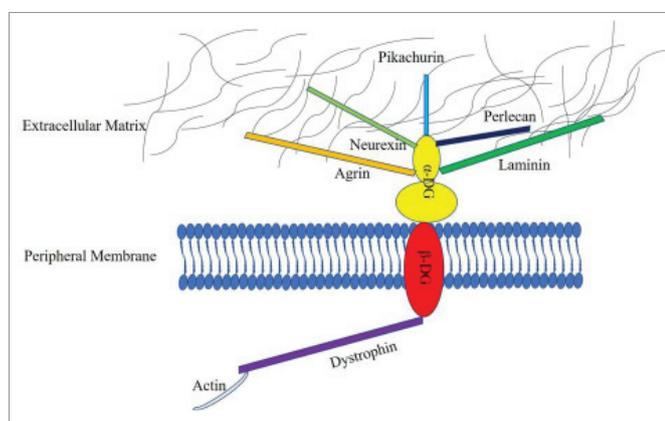


Figure 1: The Dystrophin-Glycoprotein Complex (DGC). Dystroglycan is embedded within the peripheral membrane as a pivotal member of the complex establishing multiple contacts with intracellular, transmembrane, and extracellular partners.

In humans, the hypoglycosylation of α -DG is characterized by progressive muscular dystrophy associated with brain malformation and intellectual retardation—a spectrum of recessive genetic disorders identified as α -dystroglycanopathies [15,16]. Here, we summarize findings from previous researches and derive key inferences regarding the functions of α -DG in the central nervous system.

The expression of α - dystroglycan in the central nervous system

α -DG is expressed in the intracerebral vasculature and astrocytic endfeet abutting the glia limitans in the central nervous system [17]. α -DG is also expressed by photoreceptor cells in the outer plexiform layer of the retina as well as localized at the inner limiting membrane and the basal lamina of blood vessels [18]. On the other hand, α -DG has been confirmed to be expressed in many important brain parts including all major neurons and glia in the developing central nervous system [19]. In addition to this, a previous study has confirmed α -DG presented in the developing cerebellum, in Purkinje cells, radial glia, granule cell precursors, hippocampus and Bergmann glia [20].

The effect of α - dystroglycan in the central nervous system

α -DG is a glycoprotein that undergoes mucin-type O-glycosylation, O-mannosylation, glycosyltransferase-mediated N-glycosylation, phosphorylated Omannosyl glycan bearing xylose and glucuronic acid-containing polysaccharide. Loss of N-linked glycosylation on α -DG has no effect on its ability to bind its ligand, while loss of O-linked glycosylation appears to disrupt α -DG-ligand binding ability [21]. α -DG participates as a ligand for molecules associated with the extracellular matrix such as perlecan, laminin, neurexin, agrin slit, and pikachurin *via* heavily glycosylated O-Mannose (O-Man) type sugar moieties (Figure 1) [7]. Therefore, the physical link between the cytoskeleton and the extracellular matrix is completed by the proper glycosylation of α -DG. α -DG is also essential for axon guidance, neuronal migration, Neuromuscular Junction (NMJ) formation in the central nervous system as well as the formation of optic tissue [22-24]. Therefore, the function of α -DG also includes the stabilization of the membrane structure, receptors for cell migration and differentiation and the assembly of basement membrane components [23,25].

Symptoms of α -dystroglycanopathy in central nervous system

α -Dystroglycanopathy is a group of diseases, in which the O-mannosylation of α -DG is lacking. They show mild to severe muscular dystrophy, optical anomaly, and brain anomaly. It has been confirmed that the decrease in the ligand binding capacity of α -DG to laminin on ECM typically induces α -dystroglycanopathy [15]. Decreased levels of I1H6, a specific antibody that connects laminin-



binding glycan of α -DG, has been found in α -dystroglycanopathy patients [8,10]. As the sugar moieties of O-Man glycosylation are quite complicated and extensive, the clinical spectrum of α -dystroglycanopathy phenotype is also quite broad. Generally, α -dystroglycanopathy was assumed to be a congenital muscular dystrophy [10]. The symptoms of α -dystroglycanopathy in central nervous system are dependent on the phenotypes of the brain.

The Walker Warburg syndrome (WWS), an autosomal recessive disease, is the most severe type of the diseases classified as α -dystroglycanopathy. The first WWS patient with lissencephaly was reported by Walker in 1942 [7]. WWS usually starts at an early fetal phase, with severe abnormalities in the brain tissue, such as severe lissencephaly, cobblestone cortex, agyria, hydrocephalus, absent corpus callosum, absent septum, absent cerebellar vermis, cerebellar hypoplasia, and occipital encephalocele [26]. Such patients have severe intellectual disabilities. These brain phenotypes can be observed by ultrasound during gestation prenatally. WWS are caused by mutations in one of several genes, including POMT1, POMT2, B3GALNT2, POMK, DAG1,FKTN, B4GAT1, FKR, LARGE, ISPD,POMGNT2/CTDC2/AGO61 and TMEM5. Life expectancy of WWS subjects is typically less than 3 years due to systemic complications such as heart failure and pneumonia[7,26].

The Muscle Eye Brain disease (MEB) is the second most severe type of α -dystroglycanopathy. The clinical manifestations of MEB include brain anomalies such as pachygyria, hypoplastic cerebellar vermis, and cerebellar hypoplasia, which are usually milder than those for the WWS phenotype [27]. They show severe mental retardation. MEB subjects also have more severe optic symptoms such as optic atrophy, glaucoma, retinal defects, congenital myopia, juvenile cataracts, nystagmus, and seldom achieve significant motor function. MEB is caused by mutations in one of several genes, including POMGNT1, POMT1, POMT2, GMPPB, and FKTN [28]. The life expectancy of MEB subjects is 10-30 years[7,27].

Fukuyama Type Congenital Muscular Dystrophy (FCMD), an autosomal recessive disease, is the second most common type of childhood muscular dystrophy next to Duchenne Muscular Dystrophy (DMD)[29,30]. The clinical symptoms of FCMD also are similar to those for MEB. In the central nervous system, FCMD patients have polymicrogyria of the cerebrum or type II lissencephaly, cerebellar cysts, and hypomyelination. Such patients also show insomnia (30%) and epileptic attacks (80%). The mean IQ of such patients is between 30 and 50. Some of them gradually develop an awareness of social skills. Moderate to severe mental retardation is observed in all cases. FCMD is caused by mutations in homozygous or compound heterozygous mutations of FKTN. The average life expectancy of FCMD is 20 years because of cardiac dysfunction, pneumonia, or infections [29,30].

Few reports have comprehensively verified cognitive ability in α -dystroglycanopathies, but some studies indicate impaired executive control, visuospatial attention and memory in α -dystroglycanopathy patients with minimal brain malformation or macroscopically normal brain structure [31]. More patients with α -dystroglycanopathy with milder symptoms, such as limb girdle type or only cardiomyopathy without central nervous system symptoms are not discussed here [32]. We have found the chronic social defeat stress sensitive mice showed lower level of α -dystroglycan in hippocampus and habenular nuclei than that of the control partners in a mouse model of depression (data not published) indicating that α -dystroglycan participated in chronic social defeat stress induced depression.

CONCLUSIONS AND PERSPECTIVE

Based on the above data it is reasonable to elucidate that a histological abnormality arising from dysfunction of glial α -DG and a synaptic defect from dysfunction of neuronal α -DG are largely responsible for the distinctive migration abnormalities during brain development and white matter changes. α -Dystroglycanopathy patients often present with intellectual deficits presumably caused by developmental brain malformation. However, much is still unknown about the role of DG in the central nervous system, particularly regarding its assumed functions in neurons of the thalamus, olfactory bulb, hypothalamus and brainstem [7]. Future study will focus on clinically relevant animal models to understand the basic functions of α -DG in the nervous system and design rational treatments for α -dystroglycanopathies.

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