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Review

Dystroglycan: important player in skeletal muscle and beyond

Ronald D. Cohn*

Johns Hopkins Hospital, Children's Center, McKusick-Nathans Institute of Genetic Medicine, 600 N Wolfe Street, Blalock 1008, Baltimore, MD 21287, USA

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Abstract

Dystroglycan is a transmembrane protein that connects the extracellular matrix to the cytoskeleton. Given the ubiquitous tissue expression of dystroglycan, different functional roles in various organ systems have been characterized during the past decade. More recently, aberrant glycosylation of dystroglycan has been identified as a novel pathogenetic mechanism in several forms of congenital and late onset muscular dystrophy syndromes. The current review summarizes the recent scientific achievements as they relate to the function of dystroglycan under normal and pathophysiological conditions.

Keywords: Dystroglycan; Skeletal muscle; Muscular dystrophy; Neuronal migration disorders

1. New aspects of dystroglycan function in skeletal muscle

Dystroglycan was originally isolated from skeletal muscle as an integral membrane component of the dystrophin–glycoprotein complex (DGC) [1]. In vertebrates dystroglycan is composed of alpha- and beta-subunits encoded by a single gene and cleaved into two proteins by posttranslational processing [2]. At the sarcolemma, β-dystroglycan binds intracellularly to dystrophin, which binds to the actin cytoskeleton, and extracellularly to α-dystroglycan. α-Dystroglycan, a highly glycosylated peripheral membrane protein, completes the link from the cytoskeleton to the basal lamina by binding to extracellular matrix proteins containing LamG domains, such as laminin [3], neurexin [4], agrin [5–8], and perlecan [9] (Fig. 1). In addition to dystroglycan and dystrophin, the DGC in muscle cells contains the sarcoglycan complex composed of five sarcoglycan proteins (α,β,γ,δ,ζ) and sarcospan [1,10,11]. Via dystrophin, the sarcolemmal DGC interacts with a pair of syntrophins (α1 and β1) and α-dystrobrevin within the cytosol [12–16]. The C-terminal tail of β-dystroglycan also contains a PP*XY* motif that can interact with dystrophin or caveolin-3 [17]. Recent evidence suggests that the ZZ domain of β-dystroglycan is essential for its physiological binding to dystrophin and utrophin [18]. Studies in animal models of muscular dystrophy have shown that α-dystroglycan is greatly reduced at the sarcolemma in dystrophin and sarcoglycan deficient mice [2,10,19]. These findings indicate that sarcolemmal expression of the sarcoglycans is a prerequisite for the membrane targeting and stabilization of α-dystroglycan. Though the exact function of the DGC is not entirely understood, it is thought to contribute to the structural stability of the muscle cell membrane during cycles of contraction and relaxation, thereby protecting the muscle from stress-induced membrane damage [20]. In humans, mutations in dystrophin cause Duchenne and Becker muscular dystrophy; mutations in sarcoglycans cause limb-girdle muscular dystrophy (LGMD 2C-F); and mutations in laminin α2 cause congenital muscular dystrophy [21–23]. Advances in technology have improved our understanding of dystroglycan function in skeletal muscle. Engineering of mice chimeric for dystroglycan expression in all tissues have been reported to cause muscular dystrophy [24]. Using the Cre-loxP system, mice with targeted disruption of the *DAG1* gene in differentiated skeletal muscle revealed a role for dystroglycan in muscle regeneration [25]. Mice with skeletal muscle specific loss of dystroglycan (*MCK-DG-null*) showed muscular

* Tel.: +1 410 955 3071; fax: +1 410 614 9246.
E-mail address: rcohn2@jhmi.edu

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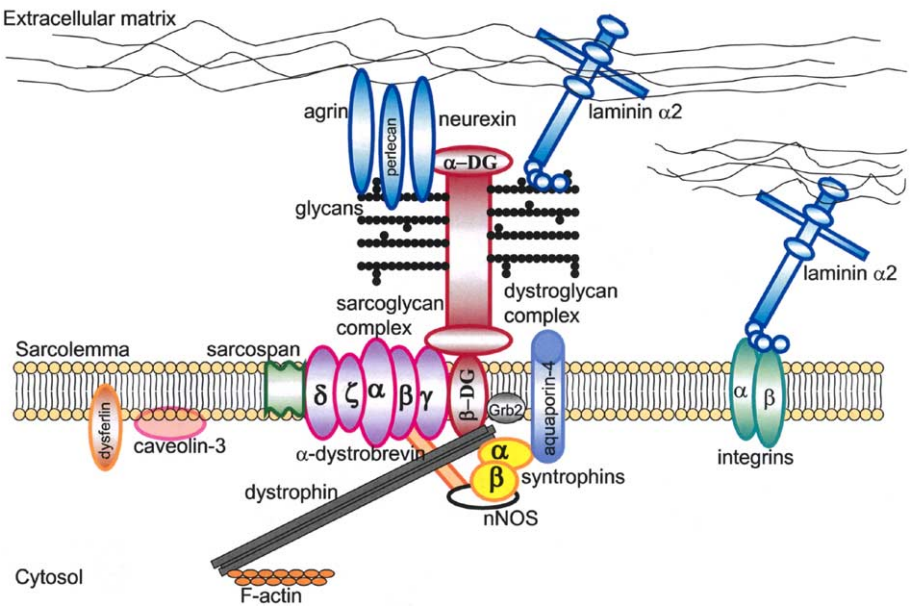

Fig. 1. The integral and peripheral components of the dystrophin glycoprotein complex and other membrane associated proteins and binding partners in skeletal muscle.

dystrophy. Interestingly, the severity of the dystrophic process was very mild and *MCK-DG-null* developed significant skeletal muscle hypertrophy, as opposed to the expected increase in adipose and fibrous tissue. The study demonstrated that maintenance of regenerating capacity by satellite cells expressing dystroglycan was likely to be responsible for the milder phenotype observed in this mouse model [25]. It has been shown that skeletal muscle seems capable of efficiently repairing itself during the early phase of the disease, and it is believed that the ongoing stimulus and activation of the repair mechanism eventually exhausts the satellite cell pool, subsequently leading to severe fibrosis and adipose tissue replacement [26,27]. The findings observed in *MCK-DG-null* mice suggest that dysfunction of the satellite cell population, resulting in impairment of the repair mechanism in skeletal muscle, represents a key mechanism in the pathogenesis of muscular dystrophy. Future efforts towards treatment should be aimed at identifying ways to maintain muscle regeneration capacity.

2. Aberrant glycosylation as a novel mechanism for neuromuscular and brain diseases

There has been a recent boom in the identification of neuromuscular diseases caused by mutations in genes that affect carbohydrate metabolism or protein glycosylation. A number of these findings relate to putative and determined glycosyltransferase enzyme defects in the *O*-glycosylation of α-dystroglycan, which subsequently led to characterization of a novel disease entity called 'dystroglycanopathies' [28–31] (Table 1).

About 500 genes are known to be involved in glycosylation processes and roughly 50% of body proteins are glycosylated [32]. Congenital disorders of glycosylation (formerly carbohydrate deficient glycoprotein syndrome, CDG) were initially identified in 1980 by Jaeken et al., [33] following the observation of abnormal processing of arylsulfatase-A and thyroxin-binding globulin in patients with severe developmental delay and neurological deficits [33]. In contrast to dystroglycanopathies, which are caused by defects in the *O*-glycosylation pathway, most syndromes of congenital disorders of glycosylation are due to abnormalities in *N*-glycosylation [32]. The following paragraphs highlight the novel discoveries of dystroglycan function in skeletal muscle and the central nervous system as they relate to *O*-glycosylation disorders.

2.1. Dystroglycan glycosylation in skeletal muscle

Dystroglycan undergoes *N*-linked and extensive *O*-linked glycosylation, and as a result α-dystroglycan migrates on SDS-PAGE as a broad band with an approximate molecular mass of 120–180 kDa, depending on tissue type (156 kDa in muscle, predicted molecular mass is ~75 kDa) [2]. α-Dystroglycan contains a large mucin-like domain with a number of Serine or Threonine residues, which are potential sites for *O*-glycosylation [2] (Fig. 2). Dystroglycan also contains four potential *N*-linked glycosylation sites, three in α-dystroglycan and one in β-dystroglycan [2]. Deficiencies of α-dystroglycan have now been described in several forms of muscular dystrophies (see below) and these findings have been mainly based on loss of immunoreactivity with one or both of the two