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Letter to the Editor

MOLECULAR MECHANISM OF SARCOLEMMA DISEASE: A SHORT REVIEW

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ABSTRACT

Genetic mutations expressing components of the dystrophin-glycoprotein complex (that attaches cytoskeleton to cell membrane, the sarcolemma) can cause several muscular dystrophies. This short literature review has been conducted to assess the molecular basis of possible mechanisms and factors which affect sarcolemma and result in muscular dystrophies. A better knowledge of mechanisms that improve sarcolemma repair could lead to new therapeutic targets in treating muscular dystrophy.

KEYWORDS: *Sarcolemma, cell, muscle, disease, apparatus*

INTRODUCTION

Skeletal muscle is a relatively well-organised organ system that develops mobility and energy metabolism in multicellular organisms. Genetic abnormalities are responsible for deteriorating muscle cell integrity resulting in gradual muscle waste with negative effects such as early mortality (1). Generally, mutations in different genes impact different muscle groups, and these disorders have been organised into many groups based on this. However, clinically diverse symptoms have been linked to mutations in various areas of the very same protein or perhaps even identical mutations (2). The underlying molecular biology processes disrupted in most of these disorders have been elucidated thanks to gene mapping investigations in families with affected members. Mutations of various proteins, and several structural proteins and enzymes that change several of these proteins post-translationally, have been linked to muscular dystrophy.

Role of proteins

Dystrophin is a large protein that anchors the sarcomere to the sarcolemma of the muscle to sustain synchronous stretching and contractions. "Duchene muscular dystrophy (DMD-d)" and "Becker muscular dystrophy" (BMD)

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are two main dystrophinopathies resulting from mutations that lead to abnormal dystrophin expression, producing asynchronous sarcomere lengthening and sarcolemma tearing (3, 4). Increased expression of utrophin, a protein comparable to dystrophin in function and structure, was found in dystrophic animal models with mutant dystrophin, likely as a key mediator for diminished dystrophin functionality (1).

The characterisation of the DMD locus product dystrophin and its localisation in the sarcolemma brought to comprehend the disease, with the identification and characterisation of the "dystrophin-associated protein complex" (4). Other muscle illnesses have been linked to a variety of novel sarcolemmal proteins. Autosomal recessive "limb-girdle muscular dystrophies (LGMD)" have been linked to mutations in any of the four "dystrophin-associated sarcoglycan subunits" (5). While "merosin-deficient congenital muscular dystrophy" has been linked to mutations in the laminin 2-chain gene (6).

The major constituents of the "skeletal muscle dystrophin-glycoprotein complex", alpha- and beta-dystroglycan, were discovered to connect dystrophin to proteins in the extracellular matrix (7). During strong muscle contractions, the dystrophin-associated complex can be considered a functional entity that reinforces the plasma membrane. Genetic mutations coding sarcolemmal proteins that aid in membrane re-sealing due to trauma, such as the dysferlin gene, trigger other muscular dystrophies. Although the caveolin-3 deficiency is sarcolemmal, it causes a change in vesicular trafficking that may have been linked to a different aetiology (8).

Dysferlin (DYSF) is also a sarcolemmal protein which might be lacking in some LGMDs patients (LGMD2B). In so many geographical locations, LGMD2B is reported to be the second most common type of dystrophy, but not everywhere (9). Massive immune cell infiltrates have been found in the muscle of dysferlinopathy patients, while dysferlin-negative monocytes have been demonstrated to be more aggressive, although macrophage adhesion and motility have been modulated. DYSF mutations are linked to various clinical manifestations, ranging from severe functional impairment to moderate late-onset forms (10). Approximately 25% of cases are clinically misinterpreted as polymyositis. The identical mutations induce "Miyoshi myopathy type 1", a distal myopathy (11). Separation of clinical phenotypes, on the other hand, is more likely to occur and is not warranted by pathological differences.

Just before initial symptoms, some individuals were quite athletic, which shows that intense strength training may alter the penetrance of DYSF mutations. As a result, regeneration appears to be slowed (12). Dysferlin plays an important role in muscle healing; hence techniques to aid membrane re-sealing in dysferlinopathy will be developed.

Biochemical signaling and molecular processes

The lack of functioning dystrophin is the biological aetiology of DMD. The other Dystrophin Glycoprotein Complex (DGC) components are reduced or absent from the muscular membrane, causing the shock-absorbing link at the sarcolemma to become disorganised. In mice, the deletion of the DGC-actin axis produces a threefold reduction in muscle elasticity (13); therefore, lateral force transfer is destabilised due to this. It increases the number and size of sarcolemmal microtears, primarily due to eccentric muscular contractions; this clarifies why big, non-hydrophobic muscle proteins can pass through the lipid bilayer, resulting in enhanced serum activity (14). Micro-tears are commonly related to inflammation and delayed onset muscle discomfort in healthy people (15). Any brief inflammatory reaction in healthy muscle regeneration is preceded by the activation and the proliferation of myoblasts, which differentiate into myocytes. They merge to generate myofibers, which have concentrated nuclei and heal the muscle. Generally, micro-tear creation and restoration of the lipid bilayer often proceed in DMD, but they gradually lead to muscle fibre loss. The inflammatory reaction becomes chronic and harmful in this instance (16).

Some investigations demonstrate the notion of Ca2+ ion passage into the cytoplasm via microtears and likely active calcium channels (17). High calcium concentrations or functional ischemia associated with loss of Nitric Oxide Synthetase (NOS) at the sarcolemma might have been the cause of nocturnal muscular cramps in DMD children following substantial day movements (14). Calcium entrance activates calpains, disrupting muscle protein homeostasis. Calpains are proteins belonging to the family of calcium-dependent, non-lysosomal cysteine proteases (proteolytic enzymes) expressed ubiquitously in mammals and many other organisms. Fibre degradation and death will result as a result of this.

Furthermore, upregulation of the calpain inhibitor calpastatin in mice model has been shown to attenuate the dystrophic process. It is simple to believe that calpain-mediated proteolysis is primarily involved in muscle atrophy.

Other processes have yet to be discovered. Excess calcium influx can cause fibre necrosis, which activates important damage pathways that eventually replace damaged muscle with connective and adipose tissue (18).

Nitric oxide (NO) is a signalling molecule that controls skeletal muscle processes such as blood circulation during contraction, force production, respiration, and glucose homeostasis. The breakdown of DGC stability delocalises NOS from the sarcolemma observed in DMD patients and dystrophic animal models. In the cytosol, it seems to be diffusely decreased (19). According to research, BMD (Becker muscular dystrophy) patients with losses of exons encoding R16/17 motifs inside the rod domain have the most severe form (20). As a result, NOS mislocalisation significantly contributes to the dystrophic phenotype by causing functional ischemia, exacerbating fatigue-mediated damage, decreasing satellite cell activation, and raising inflammatory responses (21).

A review suggests that porcine DMD models replicate human DMD disease in an accelerated phase. Immunofluorescence and Western blot analysis revealed dystrophin deficiency in DMD mutant pigs. The pigs showed a compensatory increase of utrophin, like DMD patients; mild at two days and severe at three months. The utrophin signal was limited to the vascular system in 2-day-old DMD piglets, but strong staining of the sarcolemma was detected in 3-month-old DMD pigs (22).

Role of lipid metabolism

Plasma or tissue lipid changes have been described in DMD patients (23). It was also suggested that plasma lipids play a substantial role in pathophysiology and that lipid-lowering and vascular-targeted therapy could help DMD patients (24). Statins have been described as pleiotropic medicines, meaning that in addition to decreasing cholesterol, they are known to be involved in processes linked to DMD progression, including autophagy and "NADPH oxidase 2-mediated oxidative stress". Phosphatidylcholine, sphingomyelin, cholesterol, triglycerides, and an increase in monounsaturated fatty acid species were found in the muscles of DMD patients, whereas no substantial changes in lipid metabolism were found in the muscles of BMD patients, save for lower carnitine levels (25).

Animal model of DMD with "congestive cardiomyopathy" has been widely used to explore cardiac participation in DMD (25). Only the heart, not the skeletal muscles, had a considerable reduction in total phospholipid concentration in these animals. Including both cardiac and skeletal muscles; nevertheless, the amount of phosphatidylcholine. Furthermore, DMD mice had lower activity as well as expression of "fatty acid synthase" and "stearoyl-CoA desaturase" in the liver, as well as lower insulin levels, as relative to control mice (26). Insulin insufficiency may contribute to fatty acid metabolism problems.

Role of mitochondrial impairment/dysfunction

Dystrophin deficiency causes a range of cellular stress factors by disrupting sarcolemmal stability, including cytoskeletal structure. In DMD patients and "dystrophin-deficient mouse model of DMD", increased oxidative stress, decreased handling of cellular Ca2+, and a substantial decrease in nitric oxide signalling due to defective activity of NOS have been described (27). Furthermore, cardiac remodelling switches energy expenditure from mitochondrial oxidation of long-chain fatty acids to extra-mitochondrial oxidation of carbohydrates in the early compensatory phase, which precedes clinical heart symptoms. All of these data suggest that mitochondrial metabolic changes exist in DMD hearts before the onset of cardiomyopathy (25).

CONCLUSION

The focus of this brief review was on muscular dystrophies induced by mutations in sarcolemmal as well as sub-sarcolemmal proteins. The type of sickness, the hereditary cause, and the pathological pathways that could lead to future therapeutic approaches have been summarised. Mutations in genes expressing sarcolemmal proteins cause X-linked Duchenne and Becker muscular dystrophies, as well as "autosomal recessive limb-girdle muscular dystrophies". To better understand the condition, we attempt to present a critical synthesis of what we think to be the key components.

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