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Review article

Altered membrane integrity in the progression of muscle diseases

Kevin E. McElhanon, Sayak Bhattacharya*

Department of Physiology and Cell Biology, Davis Heart and Lung Research Institute, The Ohio State University Wexner Medical Center, 473 W. 12th Ave, Columbus, OH 43210-1252, United States

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ABSTRACT

Sarcolemmal integrity is orchestrated through the interplay of preserving membrane strength and fast tracking the membrane repair process during an event of compromised membrane fragility. Several molecular players have been identified that act in a concerted fashion to maintain the barrier function of the muscle membrane. Substantial research findings in the field of muscle biology point out the importance of maintaining membrane integrity as a key contributory factor to cellular homeostasis. Innumerable data on the progression of membrane pathology associated with compromised muscle membrane integrity support targeting sarcolemmal integrity in skeletal and cardiac muscle as a model therapeutic strategy to alleviate some of the pathologic conditions. This review will discuss strategies that researchers have undertaken to compensate for an imbalance in sarcolemma membrane fragility and membrane repair to maintain muscle membrane integrity.

1. Introduction

The striated muscle cell membrane, also known as the sarcolemma, plays a crucial role in defining the cell structural and functional properties. Apart from maintaining the normal barrier function of the muscle by separating the internal cellular components from the extracellular milieu, the sarcolemma also serves key functions such as coordinating excitation-contraction coupling, transmission of chemical and electrical signals to neighboring areas and creating a platform for initiation of the signal transduction processes [1,2]. The importance of the membrane structure has been extensively reinforced by studies showing that compromised membrane integrity is a potential contributor to the inheritance of, as well as progression of several myopathies [3–5]. We summarize some of the important implications of compromised membrane integrity on muscle function and related pathology.

It is well documented that sarcolemmal integrity is established through a balance that maintains muscle membrane strength and the membrane repair process that reseals damage to restore normal membrane integrity [6,7]. As demonstrated in various studies, enhancing the membrane repair process compensates for compromised sarcolemmal fragility [8,9]. In this review, we address the strategies explored to restore membrane integrity either through improving membrane fragility or by augmenting the membrane repair process. The process of membrane repair involves interaction of various protein partners that spontaneously accelerate cellular functions like vesicular trafficking. When sarcolemmal integrity is compromised through mechanical damage in response to destabilization of the sarcolemmal architecture during myopathic conditions (mainly muscular dystrophy) [10], enhancing the membrane repair machinery is crucial to compensate for the destabilization response (Fig.1) [11–13]. This conserved membrane repair response operates in all eukaryotic cells. The sarcolemmal membrane has evolved various techniques to restore the barrier function. Vesicular endo- and exocytosis are the primary modes of “patch formation” that mount a transient response to membrane injury to reseal the membrane and protect it from further damage [14]. The canonical membrane repair response following an injury as demonstrated by several investigators, is that upon injury or damage spatial holes on the membrane allow extracellular Ca^{2+} to flood the intracellular space to trigger internal signaling events [15–17]. These events trigger intracellular vesicle migration to, and aggregation at the site of injury to initiate patch formation that remodels the damaged portion of the membrane [18–21]. This resealing mechanism exists due to the interplay of various participating proteins shown to aid in the repair process. Many studies pinpoint the main molecular players that have an integral role in maintaining membrane integrity including dysferlin, MG53 also known as TRIM72, caveolins, annexins, dystrophin and its associated glycoprotein complex, synaptotagmin and SNARE proteins, calpains, S100A10 and ESCRT machinery [17,22–30]. These repair machinery components may act singly or in a concerted fashion with other members to mediate the membrane repair response and ultimately contribute to healthy sarcolemmal integrity.

The membrane restoration response may adopt different repair measures following a segmented disruption on the membrane

* Corresponding author.
E-mail address: sayak.bhattacharya@osumc.edu (S. Bhattacharya).

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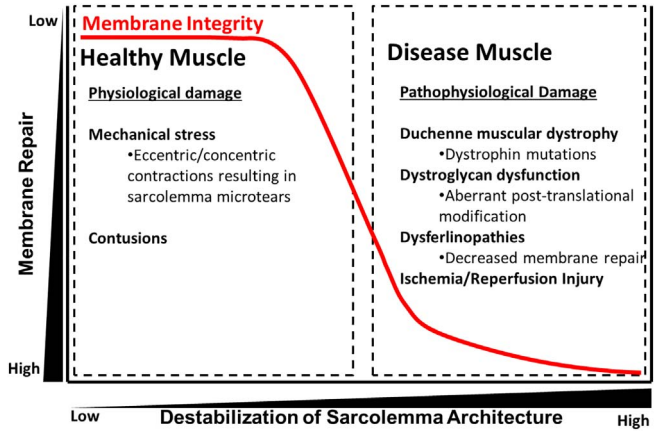

Fig. 1. Skeletal muscle diseases associated with compromised membrane integrity. Membrane integrity is a balance between the sarcolemmal repair response to injury and sarcolemmal strength imparted by a stable sarcolemmal architecture. The dystrophin-glycoprotein complex (DGC) serves to stabilize the sarcolemma by anchoring the actin cytoskeleton to the extracellular matrix. Healthy skeletal muscle is routinely injured due to the mechanical stress of contraction, however, the stabilizing function of the DGC together with the sarcolemmal repair response facilitates the quick and efficient resealing of the injury restoring barrier function and membrane integrity. Mutations that disrupt organization of the DGC increase the number and severity of these injuries. As a result, the sarcolemmal repair response is no longer sufficient to restore normal membrane integrity. The mechanical stress created during contraction is placed on the sarcolemma, resulting in membrane tears that can alter physiological homeostasis within skeletal muscle eventually leading to weakness, myofiber necrosis, and replacement of skeletal muscle with fibrotic tissue and fatty infiltrates.

depending upon the size of the disruption. Although a normal lipid bilayer would expect to reseal automatically through thermodynamic lipid-lipid interaction, the presence of a cellular cytoskeletal network imposes some degree of tension on the membrane that negates its ability to spontaneously remodel and reseal [8,14,31]. Previous studies have shown that damage to the sarcolemmal membrane induces a host of transient signaling events that recruit molecular components of the repair machinery to the site of injury to initiate patch formation. Muscle specific repair proteins such as MG53/TRIM72 and dysferlin have been given much attention over the years and are now being investigated as therapeutic targets to alleviate some of the pathology associated with myopathies resulting from compromised membrane integrity [32,33]. We have focused on the skeletal and cardiac muscle diseases that demonstrate pathology mainly due to compromised membrane fragility of the membrane and how researchers have explored ways to improve membrane integrity through compensation of compromised fragility with augmented membrane repair responses [13,34]. The review will help build an overview of the available research outcomes that can be collectively utilized to target compromised membrane integrity and integrity restoration as a therapeutic intervention for muscular diseases.

2. Skeletal muscle diseases associated with compromised membrane integrity

Perhaps the most studied diseases affecting skeletal muscle that lead to reduced membrane barrier function are the muscular dystrophies (MD). Duchenne muscular dystrophy (DMD) is the most common form, making up more than 50% of diagnosed cases of MD [35]. DMD is caused by a deficiency in functional dystrophin protein due to mutations (intragenic deletions, and less frequently duplications) in the X-linked dystrophin gene leading to destabilization of the sarcolemma architecture with a significant loss of sarcolemma strength [36–40]. In skeletal muscle, dystrophin serves to stabilize the sarcolemma by anchoring the intracellular actin cytoskeleton to the dystrophin-glycoprotein complex (DGC), which in turn interacts with laminin in the extracellular matrix. This interaction acts as a “shock absorber” to reduce the amount of mechanical stress placed on the sarcolemma during eccentric contraction by transferring sheer stress to the basal lamina [39]. One of the first studies to show that dystrophin acts to stabilize the sarcolemma during muscle contraction used a series of eccentric and isometric contractions followed by procion orange staining to evaluate the extent of muscle damage [36]. This study revealed that while both dystrophin-deficient and healthy skeletal muscle are subject to damage during contraction, extensor digitorum longus (EDL) and diaphragm muscles isolated from mdx mice displayed a greater degree of sarcolemmal injury. This finding was later confirmed in myotubes cultured from patient biopsies taken from both DMD and healthy control skeletal muscle exposed to hypo-osmotic shock to induce sarcolemmal damage [39]. Myotubes from both mdx mice expressing a truncated nonfunctional dystrophin protein and DMD patients displayed leakage of muscle specific enzymes, creatine kinase and pyruvate kinase, with increasing osmotic stress indicating that in the absence of dystrophin the sarcolemma becomes weakened due to decreased structural integrity.

In the absence of dystrophin, much of the mechanical stress created during contraction is placed on the sarcolemma, resulting in membrane tears that can alter physiological homeostasis within skeletal muscle eventually leading to weakness, myofiber necrosis, and replacement of skeletal muscle with fibrotic tissue and fatty infiltrates [41]. Mutations in the dystrophin gene are also responsible for Becker muscular dystrophy (BMD). Unlike DMD, mutations in dystrophin associated with BMD result in a truncated, partially functional protein presenting with delayed onset and reduced severity of muscle degeneration. The partially functional dystrophin protein allows the voluntary proximal muscles of the hips, pelvis, thighs, and shoulders to maintain a degree of sarcolemmal integrity and muscle function more effectively than patients with DMD, however, the heart is similarly affected [42]. In skeletal muscle, injured fibers are repaired through either satellite cell-mediated muscle fiber regeneration, or, in the case of smaller membrane disruptions, calcium-dependent vesicle exocytosis to form a membrane repair patch at the site of injury. The latter of these two mechanisms has been directly implicated in the pathology of muscular dystrophy and directly affects the balance between sarcolemmal repair and sarcolemmal strength responsible for maintaining membrane integrity.

2a. Mutations leading to pathologies due to disrupted membrane integrity

The dystrophin-glycoprotein complex (DGC) was first identified in a series of biochemical characterization studies [43-47]. cDNA cloning techniques coupled with immunohistochemistry and co-immunoprecipitation identified a complex of proteins that associate with dystrophin at the sarcolemma. Subsequent studies lead to the identification of the major proteins making up the DGC as dystroglycan α and β, which facilitate binding to laminin α2 (also known as merosin), sarcoglycans (α, β, γ, & δ), and syntrophins, which serve to strengthen the binding of dystrophin to the dystroglycan complex [48-50]. Mutations or aberrant post-translational modification of the proteins making up the DGC have been shown to lead to decreased membrane integrity in skeletal muscle. To date, mutations in the dystroglycan gene have only been identified in a small number of muscular dystrophy patients [51,52], however, dysfunction of glycosyltransferases responsible for the glycosylation of dystroglycan α/β are known to result in muscular dystrophies by disrupting the interaction of dystroglycan with laminin [53]. Mutations of protein O-mannosyltransferases POMT1, POMT2, and Large are also known to cause congenital muscular dystrophies [54-57]. Mutations of the transmembrane glycoproteins α-, β-, γ-, and δ-sarcoglycan also lead to compromised membrane integrity associated with limb-girdle muscular dystrophy (LGMD) [46,58-60] by disrupting the sarcolemmal-stabilizing function of the DGC against sheer force generated during skeletal muscle contraction [61].

Mutations in any one of the proteins making up the sarcoglycan