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Minireview Prologue

Skeletal Muscle Basement Membrane-Sarcolemma-Cytoskeleton Interaction Minireview Series*

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Kevin P. Campbell‡§ and James T. Stull¶

From the ‡Howard Hughes Medical Institute and Department of Physiology, University of Iowa College of Medicine, Iowa City, Iowa 52242 and the ¶Department of Physiology, University of Texas Southwestern Medical Center, Dallas, Texas 75390

The sarcolemma (muscle plasma membrane) plays a central role in skeletal muscle structure and function (1). In addition to the housekeeping functions of a cell plasma membrane, the sarcolemma is directly involved in synaptic transmission, action potential propagation, and excitation-contraction coupling (1). Besides these well established physiological functions, the sarcolemma, subsarcolemma cytoskeleton, and surrounding basement membrane (extracellular matrix) play an essential structural role in skeletal muscle (1–3). The biological importance of the basement membrane-sarcolemma-cytoskeleton in skeletal muscle is underscored by the number of inherited muscle diseases caused by mutations in components of the basement membrane, or cytoskeleton, or the sarcolemma protein complexes that link the basement membrane to the cytoskelton (4–8). The minireview in this and the following issues updates our understanding of the structure and function of the basement membrane, cytoskeletal costameres, and the major trans-sarcolemma links (integrins and dystroglycan) in skeletal muscle.

The basement membrane surrounds skeletal muscle fibers and is now known to be critical in muscle fiber structure and function. The skeletal muscle basement membrane is composed of the basal lamina and the reticular lamina. Basal lamina is directly linked to the sarcolemma. Genetic studies of muscular dystrophy patients and animal models of muscular dystrophy have demonstrated the importance of the basement membrane in maintenance of muscle integrity. In addition to maintenance of muscle integrity, the basement membrane is essential in the promotion of myogenesis and muscle development. Muscle regeneration is also a process that depends on the skeletal muscle basement membrane. Satellite cells (endogenous stem cells of skeletal muscle) reside between the muscle fiber and the basal lamina. Following injury, new muscle fibers regenerate within a basement membrane tube, which is believed to act as a mechanical barrier to limit migration of satellite cells, and a scaffold to orient myotube regeneration. Finally, the basement membrane is structurally and functionally specialized in areas of neuromuscular and myotendinous junctions and is required for the assembly of these structures. In the first minireview of this series entitled "The Basement Membrane/Basal Lamina of Skeletal Muscle," Joshua R. Sanes reviews the structure and function of the skeletal muscle basement membrane. In particular, he focuses on recent molecular studies that have led to a better understanding of the function of the basement membrane in skeletal muscle physiology and pathophysiology (9).

A major cytoskeletal structure in muscle that has the unique role of connecting the sarcomere to the basement membrane is the costamere. Costameres were originally described as subsarcolemma protein complexes that align in register with the Z-disk and are physically coupled to the sarcomeres. Costameres may be equivalent to focal adhesions that are expressed in non-muscle cells and are believed to be involved in the lateral transmission of contractile forces from sarcomeres across the sarcolemma to the basement membrane. In the second minireview, entitled "Costameres: the Achilles Heel of Herculean Muscle," James M. Ervasti reviews the structure and function of the striated muscle costamere (10). As with the basement membrane, the importance of the costamere for normal muscle function has been revealed by genetic studies of muscular dystrophies and dilated cardiomyopathies. Dystrophin is known to be enriched in costameres, but dystrophin is not required for costamere assembly. In the absence of dystrophin, there is a disorganization of the costameric lattice, as well as disruption of the sarcolemma integrity. Disruption of the costameric lattice correlates with functional studies that show reduction of contractile force in muscles lacking dystrophin. Ervasti's minireview provides insights into the growing costameric protein network and illustrates how these proteins can interact with many components of both the sarcolemma and cytoskeleton. In addition, the newly identified proteins suggest a role for costameric proteins in converting mechanical stimuli to alterations in cell signaling and gene expression. Finally, Ervasti discusses non-sarcolemmal mechanical defects associated with the loss of costameric proteins.

It is well recognized that the function and maintenance of skeletal muscle cell integrity is dependent upon interactions of the muscle cell with the surrounding basement membrane and underlying cytoskeleton. Trans-sarcolemma receptors are known to be involved in providing critical mechanical links between the basement membrane and the cytoskeleton. In addition, recent data suggest that these receptors transmit signals from the basement membrane into the muscle cell. Over the past 10 years there has been great progress in the identification and characterization of the two sarcolemma protein complexes that connect cytoskeleton to the basement membrane in skeletal muscle: integrins and the dystrophin-glycoprotein complex (DGC).[1]

* These minireviews will be reprinted in the 2003 Minireview Compendium, which will be available in January, 2004.

§ To whom correspondence should be addressed: Howard Hughes Medical Institute, University of Iowa College of Medicine, 400 EMRB, Iowa City, IA 52242. Tel.: 319-335-7867; Fax: 319-335-6957; E-mail: kevin-campbell@uiowa.edu; Web address: www.physiology.uiowa.edu/campbell/.

[1] The abbreviation used is: DGC, dystrophin-glycoprotein complex.

Integrins form a large family of cell surface receptors that mediate cell-extracellular matrix interactions. In the third minireview, entitled "Integrins, Redundant or Important Players in Skeletal Muscle?," Ulrike Mayer focuses on the role of integrins in skeletal muscle (11). Of the current members of this family, a subset is expressed in skeletal muscle, in particular, at the sarcolemma, neuromuscular junction, myotendinous junction, and costameres. Expression of the integrin family is regulated during skeletal muscle development. Integrins play a major role in muscle differentiation, and $\alpha_7\beta_1$ integrin is a critical receptor for myoblast migration. In adult skeletal muscle, integrins are concentrated at the neuromuscular junction and the myotendinous junction and provide an important link to the basement membrane in these specialized regions of muscle. $\alpha_7\beta_1$ integrin is the major form found in adult skeletal muscle. Integrins have also been implicated in skeletal muscle diseases, and the absence of α_7 integrin leads to a mild muscular dystrophy in both mice and humans. Myotendinous junctions were severely disturbed in mouse models with α_7 integrin deficiency. Both mouse and human studies suggest that muscle weakness arises from destruction of the myotendinous junction, rather than from compromised sarcolemma integrity. Finally, $\alpha_7\beta_1$ integrin is reduced in several muscular dystrophies, and $\alpha_7\beta_1$ integrin overexpression may provide a possible therapeutic approach for Duchenne muscular dystrophy.

In the final minireview, entitled "Dystrophin-Glycoprotein Complex: Post-translational Processing and Dystroglycan Function," Daniel E. Michele and Kevin P. Campbell focus on the major sarcolemma membrane complex in adult skeletal muscle that links the cytoskeleton to the basement membrane (12). DGC is a large oligomeric complex of proteins in the sarcolemma of skeletal muscle. The DGC is composed of both integral and peripheral membrane proteins and provides a structural connection between the basement membrane and the actin cytoskeleton and has been hypothesized to protect the sarcolemma from mechanical damage during muscle contraction. Several forms of muscular dystrophy arise from primary mutations in genes encoding components of the DGC. The DGC is grouped into three subcomplexes, dystroglycan (α- and β-dystroglycan), the sarcoglycan-sarcospan subcomplex, and the cytoskeletal components dystrophin, syntrophyin, and dystrobrevin. Michele and Campbell review the current status of our understanding of the DGC, and in particular focus on the structure and post-translational processing of dystroglycan. Interestingly, recent genetic data have demonstrated that proteins with homology similar to glycosyltransferases are linked to muscular dystrophy and appear to preferentially or exclusively modify α-dystroglycan. The role of glycosylation in the function of dystroglycan is discussed, and the mechanisms whereby the loss of functional dystroglycan leads to clinical symptoms, including muscular dystrophy, and abnormal central nervous system development and function are presented. Finally, new insights into dystroglycan function revealed from the studies of mouse models and patients with incomplete glycosylation (dystroglycanopathies) are reviewed.

Much progress has been made in our understanding of the role of basement membrane-sarcolemma-cytoskeleton interactions in the development, structure, and function of striated muscle. The field continues to be a dynamic arena for future research, in which new functional molecules, their interactions, and their functional significance, continue to be identified from molecular genetics of human diseases, biochemistry, cell biology, and gene targeting in the mouse. Given the essential role of these molecules in human disease, understanding the interactions of the skeletal muscle basement membrane-sarcolemma-cytoskeleton will hopefully lead to a better understanding of disease pathogenesis and therapeutic opportunity.

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