Contraction of skeletal muscle is an exquisite and orchestrated process that has been studied at the molecular level for more than 80 years. Although the contractile protein machinery is understood in detail, excitation, contraction, and many muscle pathologies also require understanding the critical roles of membrane systems (Figure 1).

The firing of motor nerves originating from the brain or spinal cord initiates a contraction. An action potential from a single neuron is transmitted to a group of muscle fibers (large multinucleated cells) via a chemical synapse created by vesicular release of acetylcholine at the neuromuscular junction. Acetylcholine binds to specific receptors on the muscle plasma membrane (sarcolemma), causing local Na+ inflow, which in turn triggers opening of Na+ channels throughout the sarcolemma, creating the action potential (muscle excitation). Contraction requires the participation of an additional membrane system, the sarcoplasmic reticulum, and the process of “excitation-contraction coupling,” first identified by Alexander Sandow more than 60 years ago. Depolarization of the sarcolemma travels into the interior of each muscle fiber via invaginations called t-tubules, which contain voltage-sensing proteins, the dihydropyridine receptor (DHPR), which are in close proximity to the lateral cistern of the sarcoplasmic reticulum (SR). The SR is smooth endoplasmic reticulum in muscle that surrounds each myofibril (the contractile organelles) and is the major site of calci-

**Figure 1.** Steps in skeletal muscle excitation, contraction and E-C coupling. Ach = acetylcholine; Ry = ryanodine; DHP = dihydropyridine

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um sequestration in this tissue. With depolarization, the DHPR communicates with a gated Ca^{++} release channel on the SR, the ryanodine receptor (RyR), which then opens, releasing stored Ca^{++}.

With the opening of the ryanodine channel, cytosolic calcium rises from 10^{-8} M to nearly 10^{-6} M. This increase in free calcium initiates a local chain of events, resulting in a muscle contraction. Before the calcium influx, the thick myosin filaments are sitting quietly with thin actin filaments interdigitated between them. The thick myosin filaments have oar-like projections extending toward the actin filaments with receptors at their ends. When the muscle is relaxed, the sites on the actin filaments that bind to the myosin projections are blocked by the protein complex troponin-tropomyosin (tropo from the Greek: to turn). When triggered by the calcium influx, the “tropo” complex rotates, thereby exposing the binding sites. The myosin projections then bind to the actin, forming cross-bridges. Using the energy in ATP, the actin filaments are then “rowed” toward the center of the sarcomere by the movement of the projections, producing muscle contraction. When nerve stimulation ceases, the sarcolemma repolarizes and the ryanodine channels close. Calcium returns to the SR via ATP-dependent calcium pumps in the SR membrane. With lower free cytosolic calcium, mass action leads to dissociation of calcium from troponin and rotation of troponin-tropomyosin, which releases the cross-bridge, producing relaxation. (When one dies, ATP is not available for the calcium pump to participate in relaxation and to dissociate myosin from actin; hence muscle becomes stiff, a process known as rigor mortis).

Dysfunction at various steps in the excitation–contraction process produces a set of pathological conditions. Myasthenia gravis is an autoimmune disease resulting from antibodies against the acetylcholine receptors on the sarcolemma within the neuromuscular junction. Binding of these receptor antibodies inhibits the initiation of the muscle action potential. Ensuing skeletal muscle weakness can manifest as drooping eyelids and double vision from strabismus. Other skeletal muscles (eg, respiratory) can also show evidence of weakness. Treatment can involve acetylcholinesterase inhibitors (eg, neostigmine) to increase acetylcholine levels, immunosuppressants (eg, prednisone), and plasmaphoresis to remove autoantibodies.

Malignant hyperthermia is a condition caused by mutations in the RYRI gene, which encodes for the predominant ryanodine channel isoform in skeletal muscle. These rare mutations can lead to high calcium release in response to certain volatile anesthetics (eg, halothane) and muscle relaxants (especially succinylcholine), resulting in contractures, muscle rigidity, high fever, and rhabdomyolysis, followed by renal damage and other major organ failure. These general anesthetics act by increasing the open-time of ryanodine channels. Fiber damage results from compensatory ATP consumption and ensuing depletion. Malignant hyperthermia is often fatal unless quickly treated with dantrolene, which acts to block ryanodine channel opening. In addition to many RyRI mutations, malignant hyperthermia has also been associated with a rare mutation in the t-tubule voltage sensor (DHPR). Interestingly, in this case the mutation is located in the region of DHPR, which couples to RyR1. These mutations that lead to malignant hyperthermia do not “penetrate” unless there is exposure to a triggering agent. One may speculate that DHPR or RyR1 mutations might coordinate with other factors that can lead to muscle weakness (eg, statins). Hereditary dystrophies such as Duchenne and Becker result from absent or defective dystrophin, a protein that resides beneath the sarcolemma. This defect leads to sarcolemma lesions, excessive calcium entry from the extracellular space and necrosis. The possibility that RyR1, or DHPR mutations, associated with malignant hyperthermia, might synergize with dystrophin mutations to accelerate muscle degeneration should be investigated.

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