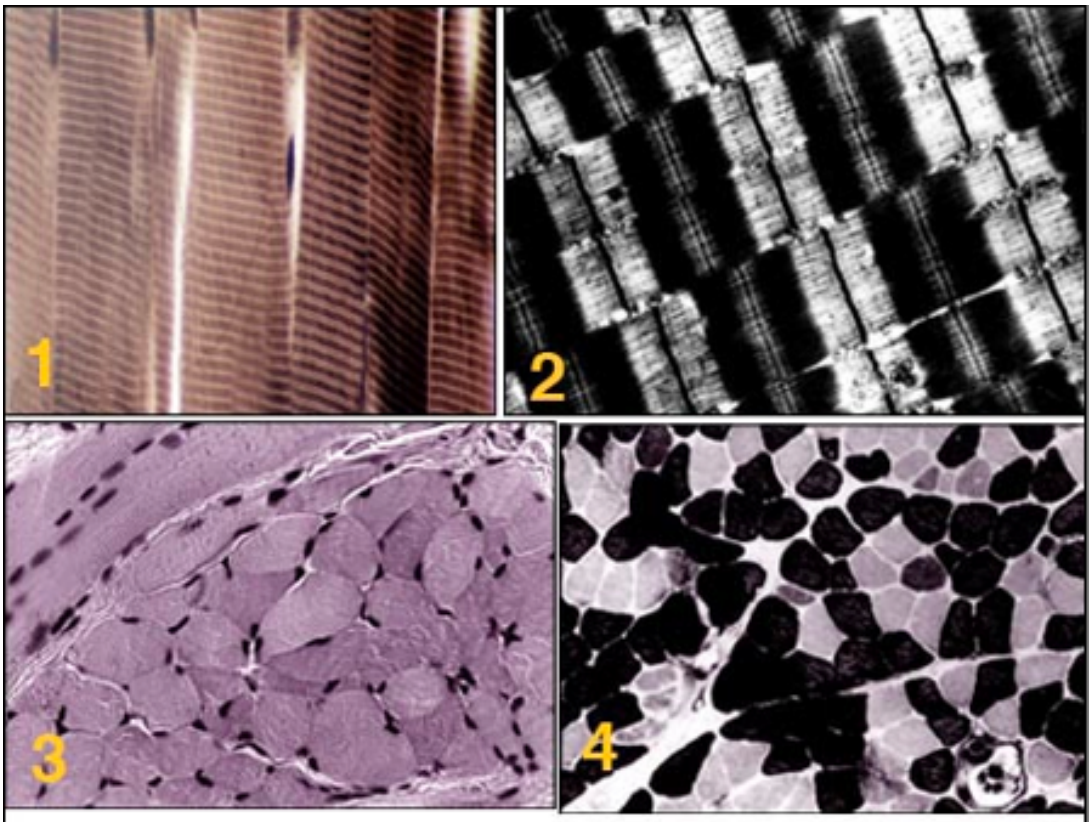
Skeletal Muscle



1. A longitudinal section of skeletal muscle cells.
2. Details of the banding on 5 myofibrils within a skeletal muscle cell.
3. Cross-sectional and longitudinal profiles of skeletal muscle cells.
4. A cross-section stained to demonstrate type 1 (light) and type 2 (dark) skeletal muscle cells.

Skeletal muscle is the most abundant tissue in the body and forms those structures generally referred to as "the muscles". Skeletal muscle makes up about 40% of the total body weight. It permits a wide range of voluntary activities from the intricate and fine movements involved in writing to the rapid, powerful forces associated with jumping or throwing a ball. The power that can be generated by skeletal muscle is illustrated by the speed attained by a thrown ball which, at the moment it leaves the fingertips, may reach speeds of over 90 mph. Muscle contraction also plays an important role in generating heat and aids in maintaining a normal body temperature of about 37˚C. The unit of structure of muscle tissue is the muscle cell, which, because of its elongated shape, also is called a fiber. Functionally, the shape of the cell is important, because a greater unidimensional contraction can be achieved by an elongated cell than by a globular cell of the same volume. Within a muscle mass, the fibers are oriented in the direction of movement.

Organization

The smallest independent unit of skeletal muscle visible with the light microscope is the fiber, which is a long multinucleated cell. Groups of parallel fibers form fascicles that can be seen with the naked eye. In turn, groups of fascicles make up an entire muscle. Fascicles vary in size with different muscles and in general are small in muscles associated with fine movements and large in muscles that perform actions demanding greater power. At all levels of organization, muscle is associated with connective tissue. The entire muscle is surrounded by a connective tissue sheath called the epimysium. Septa pass from the deep surface of the epimysium to invest each fascicle as the perimysium; delicate extensions of the perimysium wrap each fiber as the endomysium. Although given different names according to its association with different structural units of muscle, the connective tissue is continuous from one part to another. It consists of collagenous, reticular, and elastic fibers and contains several cell types including fibroblasts, macrophages, and fat cells. The endomysium is especially delicate and consists mainly of reticular fibers and thin collagen fibers; it carries blood capillaries and small nerve branches. The larger blood vessels and nerves lie within the perimysium. The connective tissue not only binds the muscle units together but also acts as a harness and aids in integrating and transmitting the force of their contractions. The amount of connective tissue varies from muscle to muscle, being relatively greater in muscles capable of finely graded movements. Elastic tissue is most abundant in muscles that attach to soft parts such as the muscles of the tongue and face.

The Skeletal Muscle Fiber (Cell)

Generally, skeletal muscle fibers do not branch, but the muscles of the face and tongue may do so where the fibers insert into mucous membranes or skin. The fibers of skeletal muscle are elongated tubes that vary in shape and length. Some are cylindrical with rounded ends and appear to extend throughout the length of a muscle; others are spindle-shaped with narrowly tapering ends and apparently do not run the length of the muscle. One end of the fiber may attach to a tendon, while the other unites with connective tissue in the belly of the muscle, or both ends may lie within the muscle mass. In transverse sections of fresh muscle the fibers are round or ovoid, but in fixed material they appear as irregular polyhedrons. The fibers range between 10 and 100 μm in diameter and my reach a length of 10 cm. The size varies from muscle to muscle and even within the same muscle. Longer fibers have the greater diameters and are associated with more powerful muscles. Some spatial arrangement of the fibers within a muscle has been noted, fibers of large diameter tending to be located more centrally. The size of the fibers changes with use, and fibers may hypertrophy (increase in size) in response to continued use or atrophy (decrease in size) with disuse.

The most outstanding structural feature of skeletal muscle fibers is the presence of alternating light and dark segments that result in the banding or cross-striations that are seen when the fiber is viewed in longitudinal section. Under polarized light, the dark bands are anisotropic and are called A bands, whereas the light bands are isotropic and thus are called I bands. Running transversely through the center of the I band is a narrow, dense line, the Z line or Z disc. In electron micrographs, a pale narrow region, the H band, can be seen transecting the A band, with a dark M line within it. The relative length of each band depends on the state of contraction of the fiber. The length of the A band remains constant, whereas the I band is prominent in a stretched muscle and short in a contracted muscle. The contractile unit of the

muscle fiber is a sarcomere, defined as the distance between two successive Z lines. Within the sarcomere, as the I band becomes shorter, the Z lines approach the ends of the A bands.

Structure of Skeletal Muscle Fibers

Each skeletal muscle fiber is an elongated cell invested by a delicate membrane that, by electron microscopy, can be resolved into the plasmalemma and an adherent outer layer of glycoproteins and glycosaminoglycans. The plasmalemma of a muscle cell is referred to as the sarcolemma but is no different from the limiting plasmalemma of any cell. The outer glycoprotein/glycosaminoglycan layer corresponds to the basal lamina of epithelia and is called the external lamina. It is associated with delicate reticular fibers that mingle with the reticular fibers of the endomysium. The striated muscle fiber is a multinucleated cell. Large skeletal muscle cells may contain several hundred nuclei. The nuclei are elongated in the direction of the long axis of the fiber and, in adult muscle, are peripheral, located immediately beneath the sarcolemma. The chromatin tends to be distributed along the inner surface of the nuclear envelope, and one or two nucleoli usually are present. The nuclei are fairly evenly spaced along the fiber but become more numerous and irregularly distributed in the area of attachment of the muscle to a tendon. Although the cytoplasm of the muscle cell is called the sarcoplasm, it corresponds to that of any cell. Many small Golgi bodies are present near one pole of a nucleus; lysosomes also usually take up a juxtanuclear position. Closely associated with the muscle fiber are satellite cells that lie flattened against the fiber covered by the same external lamina that invests the muscle cell. Although their nuclei are difficult to distinguish from muscle cell nuclei by light microscopy, they are more fusiform, more condensed, the chromatin is less dispersed, and nucleoli are lacking. The cytoplasm is scanty but may form a clear boundary between the nucleus of the satellite cell and the muscle fiber. In electron micrographs, satellite cells show centrioles (not seen in muscle cells), scant endoplasmic reticulum, a small Golgi complex, and a few mitochondria near the ends of the nuclei. Satellite cells may represent survivors of the primitive myoblasts; they account for less than 4% of the muscle-associated nuclei. Myofibrils are elongated, threadlike structures in the sarcoplasm and run the length of the muscle fiber. At 1 to 2 μm in diameter, myofibrils are the smallest units of contractile material that can be identified with the light microscope. In cross sections, myofibrils appear as small dots, while in longitudinal sections they give a longitudinal striation to the fiber. Each myofibril shows a banding pattern identical to that of the whole fiber. Indeed, the banding of the fiber results from the bands on consecutive myofibrils being in register. Cross-striations are restricted to the myofibrils and do not extend across the sarcoplasm between fibrils. The striations on adjacent myofibrils are kept in alignment by a system of intermediate filaments composed of the protein desmin which links adjacent myofibrils to each other and also links the myofibrils to the cell membrane. Associated with each myofibril is the sarcoplasmic reticulum, a modification of the smooth endoplasmic reticulum seen in other cells. In muscle, the sarcoplasmic reticulum serves as a store for calcium ions. The membrane of the sarcoplasmic reticulum contains numerous transmembrane proteins, including calcium-ATPase, that actively transport calcium from the cytosol into its lumen. Here, calsequestrin and other proteins bind and store the internalized calcium ion. This organelle consists of an extensive and continuous system of membrane-bound tubules called sarcotubules that form a mesh around each myofibril. At each junction of A and I bands, a pair of dilated sarcotubules, the terminal cisternae, pass around each myofibril and are continuous with the terminal cisternae of adjacent myofibrils. One of the pair of terminal cisternae serves an A band and the other serves an I band. From each of the cisternae, narrow, longitudinal sarcotubules extend

over the A and I bands, respectively. Over the A band, the tubules form an irregular network in the region of the H band, while in the I band a similar confluence occurs at the region of the Z line. Thus, each A and I band is covered by a "unit" or segment of sarcoplasmic reticulum. These units consist of the terminal cisternae at the A-I junctions, joined by longitudinal sarcotubules that anastomose in the region of the H and Z lines of their respective A and I bands. The sarcoplasmic reticulum shows the same structure regardless of fiber type. The pairs of cisternae at the A-I junctions are separated by a slender T-tubule, and the three structures - the T-tubule and two terminal cisternae - form the triad of skeletal muscle. T-tubules are inward extensions of the sarcolemma and penetrate into the muscle fiber to surround each myofibril. The T-tubules of one myofibril communicate with those of adjacent myofibrils to form a complete network through the fiber. The lumen of the T-tubule does not open into the cisternae but does communicate with the extracellular space at the surface of the sarcolemma. T-tubules are quite distinct from the sarcoplasmic reticulum and collectively make up the T-system. The T-system rapidly transmits impulses from the exterior of the fiber to all the myofibrils throughout the cell, thereby producing a coordinated response. Passage of electrical impulses to the sarcoplasmic reticulum results in release of free calcium ions from the sarcoplasmic reticulum into the neighboring contractile elements, bringing about their contraction. T-tubules and terminal cisternae are closely apposed. Junctional feet span the narrow gap between T-tubules and terminal cisternae, forming areas of low resistance through which impulses pass to the sarcoplasmic reticulum. In electron micrographs, the junctional feet appear as regularly spaced densities extending from the T-tubules to the terminal cisternae. These are matched by evenly spaced dimples on the cisternal membranes, corresponding to sites where the feet are located. The junctional feet are believed to be calcium ion channel proteins that extend from the terminal cisternae to voltage-sensing calcium ion channel proteins of the T-tubules. When depolarization occurs, the T-tubule channel proteins undergo a conformational change and, because of their intimate association with calcium ion channel proteins of the sarcoplasmic reticulum, the latter open, releasing calcium ions into the cytosol, initiating contraction.

Structure of Myofibrils

Under the electron microscope, the myofibril is seen to consist of longitudinal, fine myofilaments, of which two types have been identified, differing in size and chemical composition. The thick filaments are 10 nm in diameter; thin filaments have a diameter of only 5 nm. The thick filaments consist largely of myosin and are 1.5 μm long with a slightly thickened midportion and tapering ends. The midportion is smooth, whereas the ends are studded with many short projections. Myosin filaments can be dissociated into their constituent molecules, of which there are about 180 per filament, each consisting of a head and a tail. The tails of the molecules lie parallel and are so arranged that the smooth midportion of the filament consists of the tails only. The heads project laterally from the filament along its tapered ends and form a helical pattern along the filament. Most of the tail consists of light meromyosin, whereas the heads, with parts of the tails, consist of heavy meromyosin. Thin filaments are about 1 μm in length and are composed of globular subunits of actin attached end to end to form two longitudinal strands wound about one another in a loose helix. A second protein, tropomyosin, lies within the groove between the two actin strands and gives stability to the actin filament. A protein complex consisting of three polypeptides designated as troponin-T, troponin-I, and troponin-C is bound to tropomyosin at regular intervals of 40 nm. The troponin complex regulates actin and myosin binding. Troponin-T binds the troponin complex to

tropomyosin and positions the complex at a site on the actin filament where actin can interact with myosin. Troponin-I prevents actin from binding to myosin. Troponin-C binds to calcium ion. When this occurs, a conformational change occurs in the troponin complex, and myosin can now bind and interact with the actin filament. The energy needed for the cross bridging between myosin and actin is obtained from the breakdown of adenosine triphosphate (ATP) by ATPase activity located primarily in the globular heads of the myosin molecules. As a result of forming and breaking bonds between the myosin and actin filaments, actin filaments slide past the myosin filaments, and the length of each sarcomere is reduced, resulting in an overall shortening of each myofibril. The arrangement of the thick and thin filaments is responsible for the banded pattern on the myofibrils. The I band consists only of thin filaments, which extend in both directions from the Z line. The filaments on one side are offset from those of the other, and connecting elements appear to run obliquely across the Z line to create a zigzag pattern. As the actin filament nears the Z line, it becomes continuous with four slender threads, each of which appears to loop within the Z line and join a thread from an adjacent actin filament. Several accessory proteins (α-actinin, Z protein, filamin, and amorphin) have been identified in the Z line. α-actinin binds the actin filaments to the Z line. An additional accessory protein, nebulin, is associated with the actin-containing thin filaments. The A band consists chiefly of thick filaments (myosin) with slender cross-connections at their midpoints, which give rise to the M line. A protein, myomesin, in the region of the M line holds the myosin filaments in register and maintains a three-dimensional spatial arrangement. Another myosin-binding protein, C protein, runs parallel to the M-line in the outer region of the A band and also aids in holding the myosin myofilaments in register. Titin (connectin) is an exceptionally large accessory protein with elastic properties. It is the largest molecule found in mammalian cells. The titin molecule spans the distance between the Z line and the M line and is thought to function as a molecular spring for the development of a reactive force during stretch of a non-activated muscle. Titin, together with the connective harness enveloping the skeletal muscle cell, resist forces that would pull actin filaments out from between the myosin filaments making up the A band. Recent evidence also suggests that titin may be involved in intracellular signal transduction pathways. Actin filaments extend into the A bands between the thick filaments; the extent to which they penetrate determines the width of the H band (which consists only of thick filaments) and depends on the degree of contraction of the muscle. Each myosin filament is associated with six actin filaments. At the ends of the A bands, where the thick and thin filaments interdigitate, the narrow space between filaments is traversed by cross-bridges formed by the heads of the myosin molecules. Muscle function depends on a precise alignment of actin and myosin within each myofibril. This is achieved by accessory proteins, which attach to different components of the contractile mechanism and holds them in register with each other. The arrangement of the filaments also establishes the ultrastructural basis of the contractile mechanism. During contraction, the A band remains constant in length, the length of the I and H bands decreases, and the Z lines approach the ends of the A bands. The changes result from alterations in the relative positions of the thick and thin filaments. No change in the lengths of the filaments is involved; the actin filaments slide past the myosin filaments to penetrate more deeply into the A band. As a result, the I and H bands become shorter. The Z lines are drawn closer to the ends of the A bands, thereby decreasing the length of each sarcomere (the distance between successive Z lines) to produce an overall shortening of the myofibrils. The sliding action of the filaments results from repeated "make and break" attachments between the heads of the myosin molecules and the neighboring actin filaments. The attachments are made at sites progressively further along the actin filaments, causing the filaments to slide past one another. The force resulting in movement of the filaments appears

to be generated as the heads of the myosin change their angle of attachment to the actin filaments. To translate the contraction of the sarcomere to contraction of an entire fiber, each sarcomere in the fiber must contract simultaneously and not in sequence. This simultaneous contraction - not only in a single fiber but throughout an entire muscle - is brought about by the T-system. The force of muscle contraction is transmitted to the extracellular matrix through a series of link proteins. Actin filaments are attached to a protein known as dystrophin. Dystrophin is linked to several glycoproteins, which form a complex that passes through the plasmalemma. The outer surface of the glycoprotein complex is linked to a protein component in laminin known as laminin 2 (merosin) found in the external laminae of skeletal muscle cells. It is by this linkage that the contractile forces generated inside the skeletal muscle cell are transferred to the external lamina which in turn is united via molecular bonding into the connective tissue harness formed by interconnections of endomysium, perimysium and epimysium. Dystrophin is concentrated beneath the plasmalemma at the ends of the skeletal muscle cells at or near muscle/tendinous junctions. An inherited muscle disease known as Duchenne's muscular dystrophy that affects male children, results from a defect in the gene coding for the linking protein, dystrophin.

Fiber Types in Skeletal Muscle

Some skeletal muscles appear redder than others, reflecting the type of fibers (cells) present. Muscle fibers have been classed as red, white, and intermediate from their gross appearance or as type 1, IIA, IIB, and IIC on the basis of their histochemical staining reactions. Type I fibers are red fibers. These contain abundant myoglobin (a pigment similar to hemoglobin) and fat and are surrounded by many capillaries. They have numerous small mitochondria, are rich in oxidative enzymes, are low in myophosphorylase and glycogen, and metabolically are aerobic. Aerobic glycolysis involves the conversion of glucose to carbon dioxide and water. The mitochondria are aggregated beneath the sarcolemma and form rows between myofibrils; they possess many closely packed cristae. The Z line is wide. The fibers do not stain when reacted for adenosinetriphosphatase (ATPase) at pH 9.4 but show "reversal" and stain well (dark) when reacted at pH 4.6 or 4.3. Physiologically, type I fibers represent slow twitch fibers adapted to slow, repetitive contractions and are capable of long, continued activity. Type I fibers tend to be located deep in a muscle, closer to bone, and are common in antigravity muscles such as longitudinal muscles of the back. Type IIA fibers also are red due to abundant myoglobin but contain less fat than type I fibers. They contain much glycogen and show both aerobic and anaerobic metabolism. Oxidative enzymes are present, but their activity is slightly lower than in type I fibers. Myophosphatase activity is high, mitochondria are large but few in number, and Z lines are wide. ATPase activity is high (the fibers stain darkly) at pH 9.4 but is poor at pH 4.6 or 4.3. Type IIA fibers are considered fast twitch, fatigue resistant muscle cells. Type IIB fibers are white in color and contain moderate amounts of glycogen but little myoglobin or fat. They are distinguished by their large diameters, poorer blood supply, decreased number of large mitochondria, and narrow Z lines. The fibers are rich in myophosphorylase but poor in oxidative enzymes. Metabolically, they are anaerobic. Anaerobic glycolysis involves the conversion of glucose to lactate. After preincubation at pH 9.4, type IIB fibers show high ATPase activity but fail to stain at pH 4.3 and show only moderate reactivity at pH 4.6. Type IIB fibers represent fast twitch fibers adapted for rapid, short-lived activity as in the extraocular muscles of the eye. In comparison with types I and IIA fibers, type IIB fibers fatigue quickly. Type IIC fibers also have been described. They appear to be similar to type IIB fibers except that their ATPase activity is inhibited only at a pH lower than

4.0. They have narrow Z lines and correspond to the intermediate fiber type. Type IIC fibers represent a fast twitch muscle fiber that is more resistant to fatigue than the type IIB fiber. Type IID fibers also have been characterized.

Tendon and Tendon-Muscle Junctions

Tendons consist of thick, closely packed collagen bundles. Surrounding each bundle is a small amount of loose, fibroelastic connective tissue, the endotendineum. Variable numbers of collagen bundles are collected into poorly defined fascicles wrapped in a somewhat coarser connective tissue called the peritendineum. Groups of fascicles form the tendon itself, which is wrapped in a thick layer of dense irregular connective tissue, the epitendineum. The only cells present in the tendon are fibroblasts arranged in columns between the collagen fibers. Tendons are classic examples of dense regular connective tissue. Where muscle and tendon join, the connective tissue of the endomysium, perimysium, and epimysium becomes strongly fibrous and blends with the connective tissue of the tendon. On the muscle side of the junction, the connective tissue fibers extend into indentations of the sarcolemma and are firmly attached to the external lamina, to which the sarcolemma also attaches. Within the muscle fiber, the actin filaments of the last sarcomere are anchored to the sarcolemma at the end of the fiber. Thus, contraction of the muscle fiber is passed to the sarcolemma, the external lamina, and, by way of the connective tissue sheaths, to the tendon.