7.2.1

Gross and Microscopic Structure

Each skeletal muscle cell, also called a **muscle fiber**, develops from many individual embryonic **myocytes** that fuse into one long multi–nucleated skeletal muscle cell. The resultant fused muscle fiber is the length of the entire muscle. The longest muscle fiber in the body belongs to the sartorious muscle on the leg. These muscle fibers are bound together into bundles, or **fascicles**, and are supplied with a rich network of blood vessels and nerves. The fascicles are then bundled together to form the intact muscle. Muscle fibers are the same diameter as hair follicles. As you look down at your bicep, visualize small strands of hair follicles extending from your shoulder to the radius bone in your forearm. Clearly, one hair follicle would be too fragile to move your arm, but hundreds of millions are very adequate! Let's dissect a skeletal muscle, beginning with the muscle as a whole externally and continuing internally down to the submicroscopic level of a single muscle cell. In an intact skeletal muscle, a rich network of nerves and blood vessels nourish and control each muscle cell. These muscle fibers are individually wrapped and then bound together by several different layers of fibrous connective tissue.

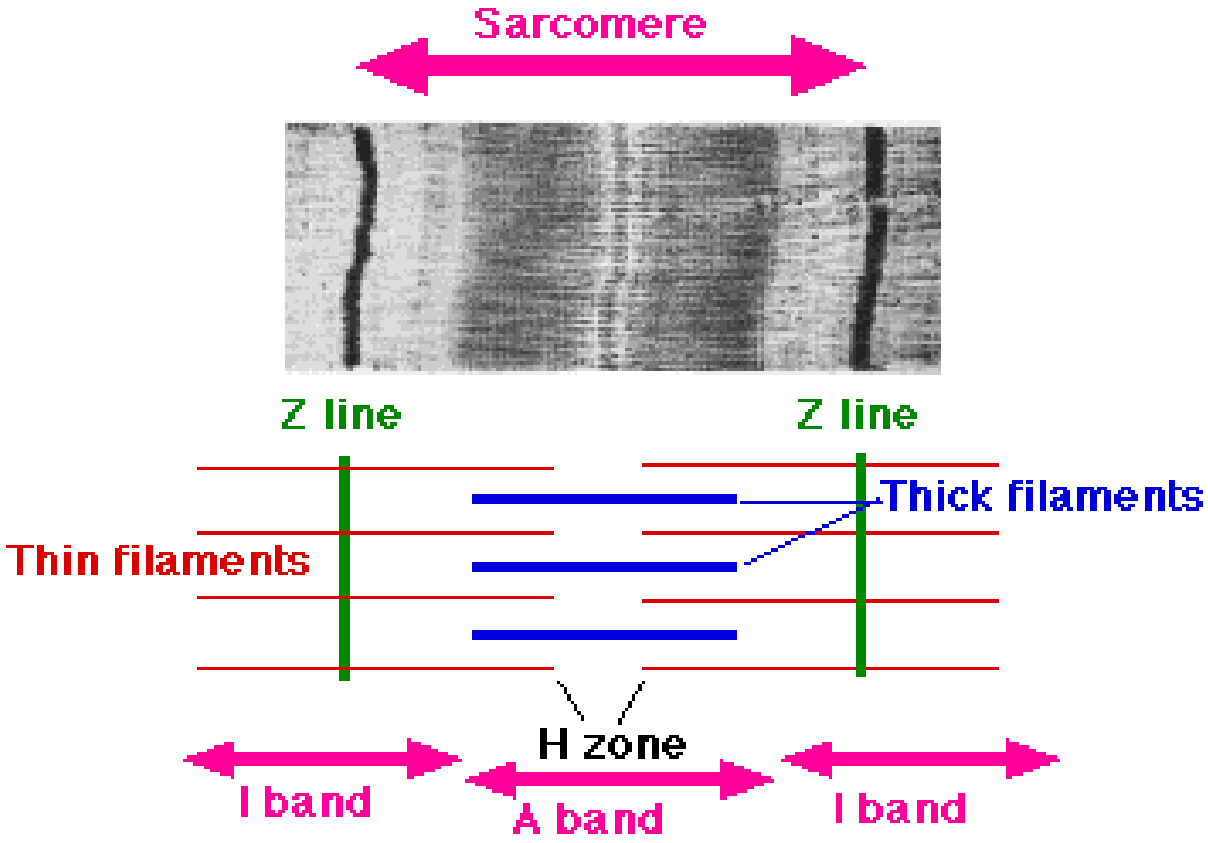
The **epimysium** (*epi* means “outside,” and mysium means “muscle”) is a layer of dense fibrous connective tissue that surrounds the entire muscle. This layer is also often referred to as the **fascia**. Each skeletal muscle is formed from several bundled fascicles of skeletal muscle fibers, and each fascicle is surrounded by **perimysium** (*peri* means “around”). Each single muscle cell is wrapped individually with a fine layer of loose (areolar) connective tissue called **endomysium** (*endo* means “inside”). These connective tissue layers are continuous with each other, and they all extend beyond the ends of the muscle fibers themselves, forming the **tendons** that anchor muscles to bone, moving the bones when the muscles contract.

Deep to the endomysium, each skeletal muscle cell is surrounded by a cell membrane known as the **sarcolemma** (you will see the prefixes *sarc-* and *myo-* quite a bit in this discussion, so you should understand that these are prefixes that refer to "muscle"). The cytoplasm, or **sarcoplasm**, contains a large amount of *glycogen* (the storage form of glucose) for energy, and **myoglobin** (a red pigment similar to hemoglobin that can store oxygen). Most of the intracellular space, however, is taken up by cylindrical (rod-like) **myofibril** protein structures. Each muscle fiber contains hundreds or even thousands of myofibrils that extend from one end of each muscle fiber to the other. These myofibrils take up about 80% of the intracellular space and are so densely packed inside these cells that mitochondria and other organelles get sandwiched between them while the nuclei get pushed to the outside and are located on the periphery, right under the sarcolemma.

Each myofibril is comprised of several varieties of protein molecules that form the **myofilaments**, and each myofilament contains the contractile segments that allow contraction. These contractile segments are known as **sarcomeres** (*sarc-* means “muscle,” and *mere* means “part”). The striations seen microscopically within skeletal muscle fibers are formed by the regular, organized arrangement of myofilaments—much like what we would see if we painted stripes on chopsticks and bundled them together with plastic wrap, with the plastic wrap representing the sarcolemma.

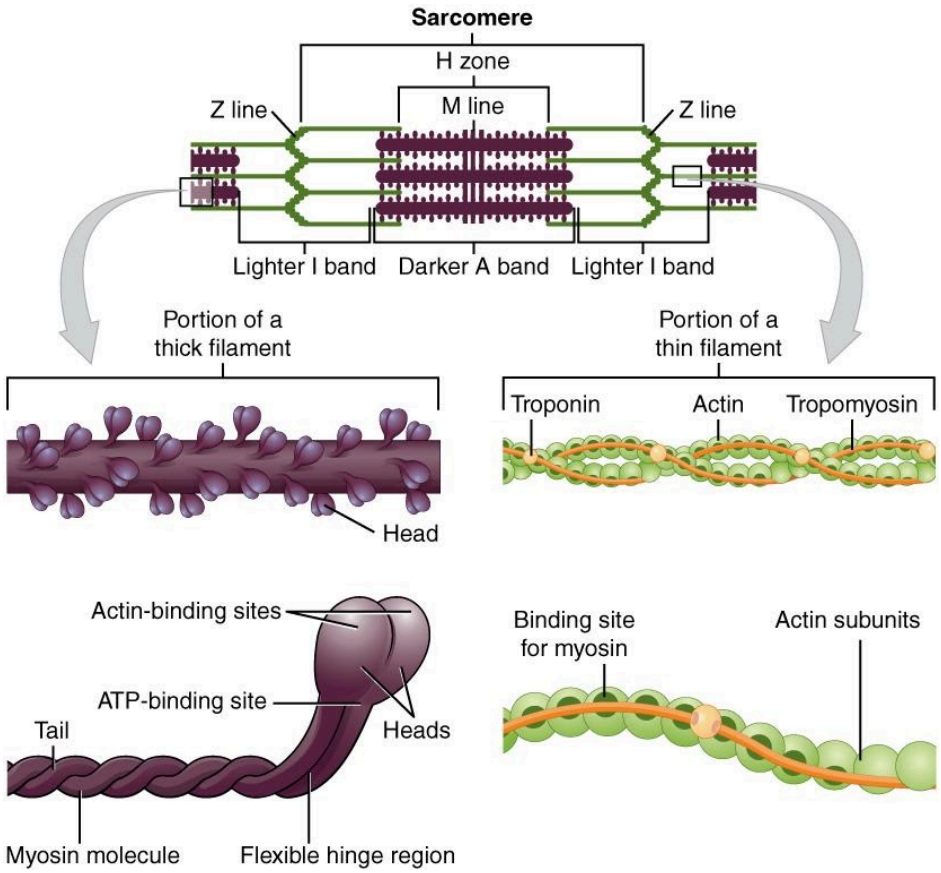
The striations microscopically visible in skeletal muscle are formed by the regular arrangement of proteins inside the cells. Notice that there are light and dark striations in each cell. The dark areas are called **A bands**, which is fairly easy to remember because "A" is the second letter in "dark." The light areas are called **I bands** and are also easy to remember because "i" is the second letter in "light." ("A" actually stands for *anisotropic*, and "I" stands for *isotropic*. Both of these

terms refer to the light absorbing character of each band. However, we'll stick to A and I bands.) The image below shows a micrograph of a sarcomere, along with a drawing representing the different parts of the sarcomere.



Skeletal Muscle Sarcomere: Thick and Thin Filaments, Z Line, H Zone, I & A Bands. *File:Sarcomere.gif; Author: Sameerb; Site: https://commons.wikimedia.org/wiki/File:Sarcomere.gif; License: Public Domain, No restrictions*

Notice that in the middle of each I band is a darker line called the **Z line** or **Z disc**. The Z lines are the divisions between the adjacent sarcomeres. Sarcomeres are connected, end to end, along the entire length of the myofibril. Also, in the middle of each A band is a lighter **H zone** (H for *helle*, which means "bright"), and each H zone has a darker **M line** (M for "middle") running right down the middle of the A band.



Sarcomere: Detailed Illustration of Thick and Thin Filaments: Title: 1003_Thick_and_Thin_Filaments.jpg; Author: OpenStax College; Site: https://books.byui.edu/-fuq;
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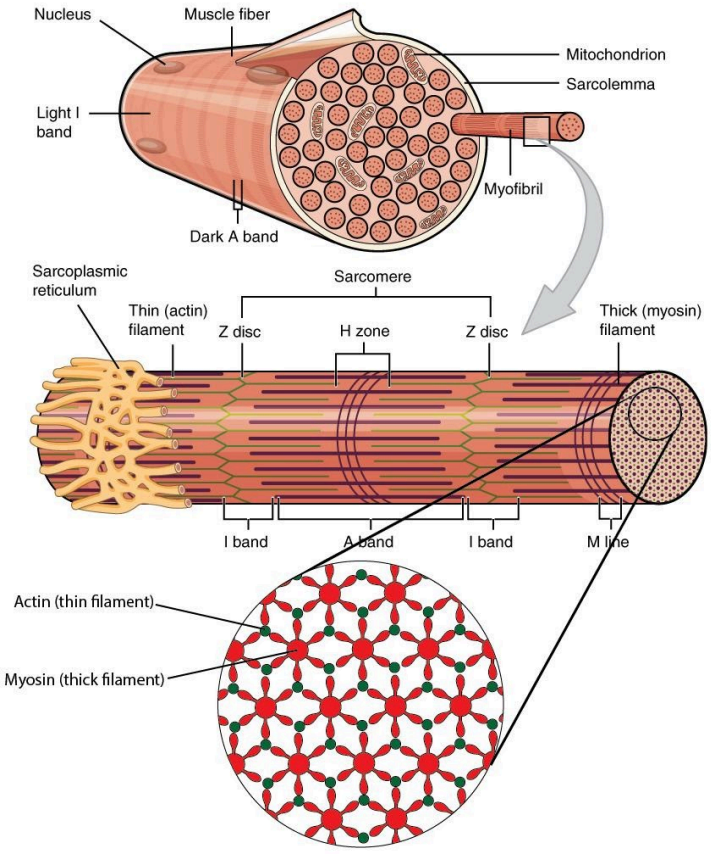
Each myofibril, in turn, contains several varieties of protein molecules, called **myofilaments**. The larger myofilaments, known as **thick myofilaments**, are made of the protein **myosin**, and the smaller **thin myofilaments** are chiefly made of the protein **actin**.

Let's discuss each myofilament in turn. Each actin molecule is composed of two strands of *fibrous actin (F-actin)* and a series of **troponin** and **tropomyosin** molecules. Each F-actin is formed by two strings of *globular actin (G-actin)* wound together in a double helical structure, much like twisting two strands of pearls with each other. Each G-actin molecule would be represented by a pearl on our hypothetical necklace. Each G-actin subunit has a binding site for the myosin head to attach to the actin. **Tropomyosin** is a long string-like polypeptide that parallels each F-actin strand and functions to either hide or expose the "active sites" on each globular actin molecule. Each tropomyosin molecule is long enough to cover the active binding sites on seven G-actin molecules. These proteins run, end to end, along the entire length of the F-actin. Associated with each tropomyosin molecule is a third polypeptide complex known as **troponin**. Troponin complexes contain three globular polypeptides (*Troponin I, Troponin T,* and *Troponin C*) that have distinct functions. Troponin I binds to actin, troponin T binds to tropomyosin and helps position it on the F-actin strands, and troponin C binds calcium ions. There is one troponin complex for each tropomyosin. When calcium binds to troponin C, it causes a conformational change in the entire complex that results in exposure of the myosin binding sites on the G-actin subunits. More on this later.

The thick myofilaments are composed chiefly of the protein **myosin**, and each thick myofilament is composed of about 300 myosin molecules bound together. Each myosin is made up of six protein subunits, two *heavy chains* and four *light chains*. The heavy chains have a shape similar to a golf club, having a long shaft-like structure, to which is connected the globular myosin head. The shafts, or tails, wrap around each other and interact with the tails of other myosin molecules, forming the shaft of the thick filament. The globular heads project out at right angles to the shaft. Half of the

myosin molecules have their heads oriented toward one end of the thick filament, and the other half are oriented in the opposite direction. It is the myosin heads that bind to the active sites on the actin. The connection between the head and the shaft of the myosin molecules function as a hinge and as such is referred to as the **hinge region**. The hinge region can bend and, as we shall see later, creates the power stroke when the muscle contracts. The center of the thick filament is composed only of the shaft portions of the heavy chains. Additionally, each myosin head has an ATPase that binds to and hydrolyzes ATP during muscle contraction. It is the ATP that provides the energy for muscle contraction. Each of the myosin heads is associated with two myosin light chains that play a role in regulating the actions of the myosin heads, but the exact mechanism is not fully understood. The three-dimensional arrangement of the myosin heads is very important. Imagine that you were looking at a thick filament from the end, and there is a myosin head sticking straight up. As you moved around the circumference of the thick filament, you would see myosin heads every 60 degrees. This allows each thick filament to interact with six thin filaments. Likewise, each thin filament can interact with three thick filaments. This arrangement requires that there be two thin filaments for every thick filament in the myofibril (see image below).



Muscle Fiber Detailed Diagram. Adapted from the following image: Title: 1022_Muscle_Fibers_(small).jpg;Author: OpenStax College; Site: https://books.byui.edu/-fuq;License: licensed under a Creative Commons Attribution 4.0 License.

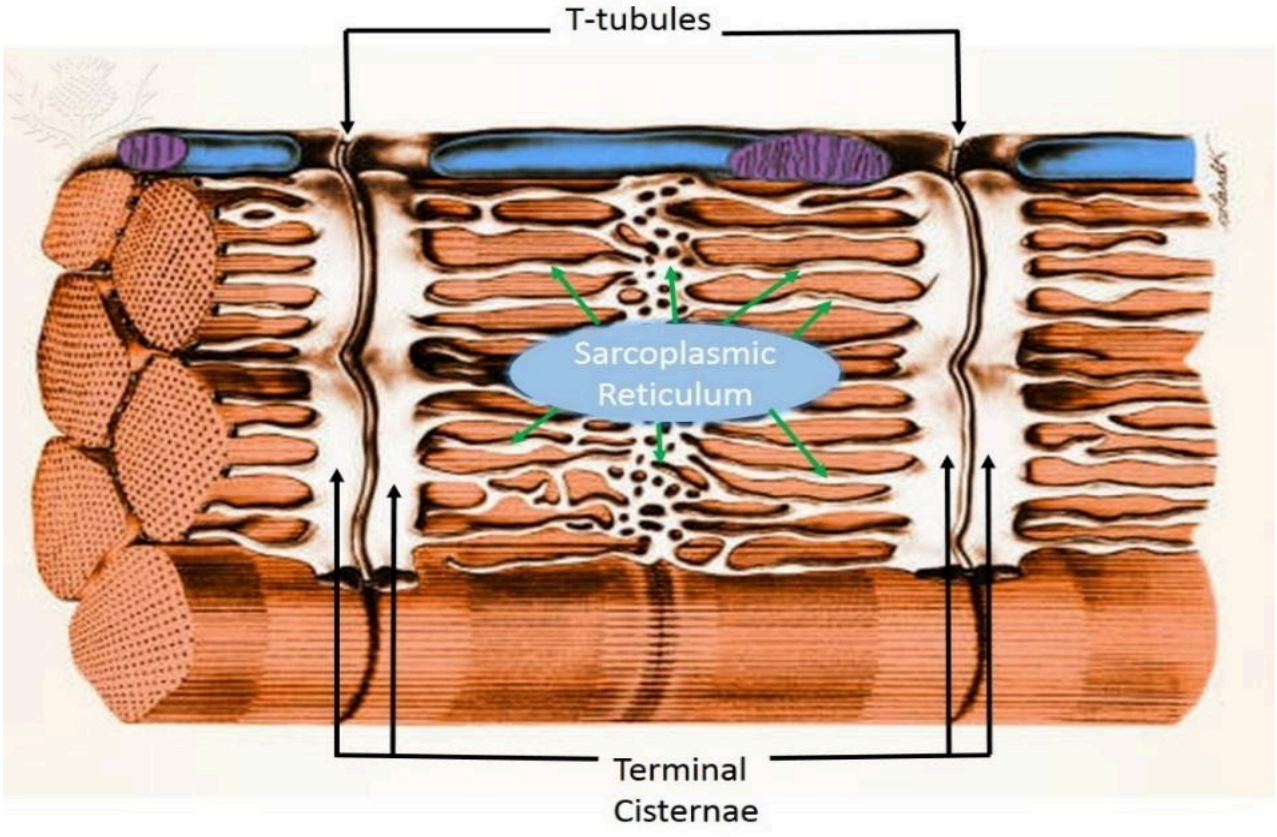
During muscle contraction, the myosin heads link the thick and thin myofilaments together, forming **cross bridges** that cause the thick and thin myofilaments to slide over each other, resulting in a shortening of each sarcomere, each skeletal muscle fiber, and the muscle as a whole—much like the two parts of an extension ladder that slide over each other. To summarize, in order for the shortening of the muscle to occur, the myosin heads have three important properties: 1.) The heads can bind to active sites on G-actin molecules, forming *cross bridges*. 2.) The heads are attached to the rod-like portions of the heavy myosin molecules by a *hinge region* as already discussed. 3.) The heads have *ATPase* enzymes that can break down ATP, using the resulting energy to bend the hinge region and allow detachment of the myosin heads from actin.

The Z-line (or Z-disc) is composed of proteins (**alpha actinin**) which provide an attachment site for the thin filaments. Likewise, the M-line is composed of proteins (**myomesin**) that hold myosin molecules in place and creatine kinase enzymes (explained later). The A band is formed by myosin molecules, and the I band is the location where thin filaments do not overlap the thick filaments. The H zone is that portion of the A band where the thick and thin filaments do not overlap.

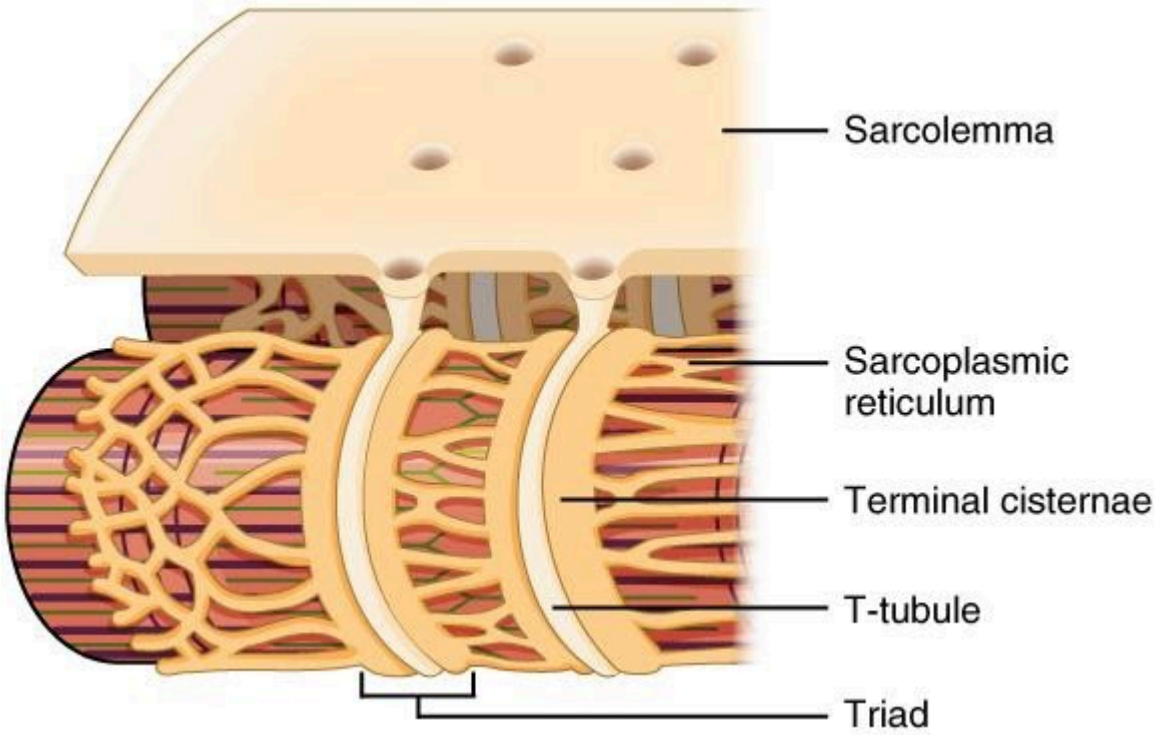
There is another important structural protein that extends from the Z disc to the M line, running within the thick filament. Due to its large size, this protein is called **titin** (titin is the largest known protein in the human body and has roughly 30,000 amino acids). It forms the core of the thick myofilaments, holding it in place, and thus keeps the A band organized. In addition, titin has the ability to stretch and recoil. It functions to prevent overstretching and damage to the muscle and to return the muscle to its normal length when it is stretched beyond its normal resting length. Recall that one of the properties of muscle is its elasticity. Titin is the protein responsible for this property.

There are several other important structural proteins, but we will only discuss one more: **dystrophin**. Dystrophin is a protein located between the sarcolemma and the outermost myofilaments. It links actin to an integral membrane protein, which, in turn, links the muscle cell to the endomysium of the entire muscle fiber. Without dystrophin the muscle will be able to contract (shorten) but no force (ie., limb movement) can be generated. Genetic mutation of the gene coding for dystrophin is one of the root causes of a class of muscle diseases known collectively as *muscular dystrophy (MD)*. The most common form of MD is Duchene muscular dystrophy (DMD), which is inherited in a "sex-linked" fashion and affects boys. Most DMD patients become wheelchair bound early in life, usually by age 12 or so. Difficulty breathing usually becomes problematic by age 20 and sadly is often the cause of their premature death.

Sarcoplasmic Reticulum and T Tubules



Sarcoplasmic Reticulum. *© 2013 Encyclopædia Britannica, Inc. Downloaded and labeled from image quest BYU-Idaho 2013.*



T-Tubule. *Title: 1023_T-tubule.jpg; Author: OpenStax College; Site: http://cnx.org/contents/6df8aab3-1741-4016-b5a9-ac51b52fade0@3/Skeletal-Muscle; License: licensed under a Creative Commons Attribution 4.0 License.*
There are two sets of tubules within skeletal muscles fibers that carry out critical functions during muscle contractions: the sarcoplasmic reticulum and the T-tubules.

T-tubules (transverse tubules) are invaginations, or indentations, of the sarcolemma. They are formed much like poking holes with a fork in your raw potato before cooking it. T-tubules communicate with the extracellular space and are filled with extracellular fluid. They are located on the sarcomere at the point where the A band and I band overlap. The T-tubules are flanked on either side by dilated regions of the cell's endoplasmic reticulum—the sarcoplasmic reticulum.

Sarcoplasmic reticulum (SR) is an elaborate network of smooth endoplasmic reticulum that surrounds and encases each myofibril, much like a loosely knitted sweater that covers your arms. It stores calcium which can then be released into the sarcoplasm when an action potential is conducted along the sarcolemma of the T-tubule. Most of the sarcoplasmic reticulum runs parallel to the myofibrils, but there are right-angle enlargements of the SR at the A band/I band junctions that flank the T-tubules. These enlargements are known as **terminal cisternae** ("end sacs") (see the image above). One T-tubule along the` two terminal cisternae that parallel it form the **triad**. The triad is critical in skeletal muscle function. At each triad, the T-tubule membrane contains large numbers of voltage-dependent proteins called dihydropyridine (DHP) channels or L-type calcium channels. Although these are called channels, they do not allow calcium to move through them; rather, they are physically linked to calcium release channels on the terminal cisternae known as ryanodine receptor channels (RyR). When the membrane is depolarized by an action potential, the DHP channel detects a depolarization and causes the RyR channels to open, resulting in the release of calcium from the terminal cisternae of the SR.