MUSCLE TISSUE

- Muscle tissue is characterized by its well-developed properties of contraction.
- Muscle is responsible for the movements of the body and the various parts of the body.
- Muscle develops from embryonic mesoderm (with the exception of myoepithelium).

Muscle is classified into 3 categories according to morphology and physiological function:

- **Skeletal Muscle**
- **Cardiac Muscle**
- **Smooth Muscle**

Specific nomenclature associated with muscle commonly involves the prefix **sarco-** or **myo-** .

The cytoplasm of muscle fibers or cells is called **sarcoplasm**.
The endoplasmic reticulum of fibers or cells is called **sarcoplasmic reticulum**.
The plasmalemma of fibers or cells is called the **sarcolemma**.

Individual muscle cells are called **myocytes**.

SKELETAL MUSCLE

Skeletal muscle, also known as **striated** or **voluntary muscle**, comprises some 40-50% of the body mass in adults and constitutes part of the largest organ system of the body.

During embryonic development **mesodermal cells** differentiate into uninuclear **myoblasts**, which elongate and fuse together to form **myotubes**, which further develop into the mature muscle fibers or **myofibers**. These myofibers are the basic units of skeletal muscle and are up to 30 cm in length. Myofibers possess large numbers of elongated or oval nuclei at their periphery, close to the **sarcolemma**. These myofibers are **syncytia** (multinucleated post-mitotic structures in which the nuclei have lost the ability to synthesize DNA). After regular staining myofibers are seen to have periodic cross striations (the source of the name "striated muscle"). A further cell-type, known as **satellite cells,** may be found adjacent to the sarcolemma. These are elongated, poorly-differentiated cells that are very difficult to discern in typical preparations, but become active during repair and regeneration processes after muscle injury.

Connective tissue arrangements of skeletal muscles

In skeletal muscles the myofibers are bound together in a similar manner to wires in a telecommunications cable. The connective tissue in the muscle serves to bind and integrate the action of the various contractile units. A thin and delicate conntissue layer, known as the **endomysium**, surrounds each individual myofiber. Myofibers are grouped together in bundles or **fascicles**, which are also surrounded by connective tissue, known as the **perimysium**. The fascicles are surrounded and bound together by a further connective tissue coating known as the**epimysium**. All these connective tissue coatings (endomysium, perimysium and epimysium) contain collagen fibers, elastic fibers, fibroblasts and are richly vascularized. The ends of skeletal muscles are attached to bones, cartilage or ligaments by means of tendons. The attachment that moves the least is known as the tendon of origin, whereas the other tendon is known as the tendon of insertion. The flattened skeletal muscles have strong flattened sheets of tendon-like tissue at their ends known as aponeuroses.

Light microscopy of myofibers

Longitudinal sections of skeletal muscle fibers show repeated cross-striations after regular staining (H&E). The stained bands are called **A-bands**, and in between these are non-stained **I-bands**. If the same myofiber is examined by polarizing microscopy the A-bands are seen to be **birefringent** or **anisotropic** (bright against a dark background with crossed polars), whereas the I-bands are **non-birefringent** or **isotropic**. (The origin of the nomenclature comes from these polarizing properties: **A** = **A**nisotropic, **I** = **I**sotropic).

At higher magnifications it is possible to see a line in the middle of the I band, known as the **Z line**.

Examination of a myofiber at high magnification shows that that it is composed of many parallel **myofibrils**. The A and I bands and Z lines are visible in the myofibrils. The unit between two Z lines is known as the **sarcomere**. The myofibrils consist of repeating strings of sarcomeres. The sarcomeres in adjacent myofibrils tend to be located in parallel, resulting in the overall cross-striations of the myofibers. It is also possible in some cases to distinguish a less-stained region in the middle of the A-bands, known as the **H-band** (Hensen's band). The sarcomeres form the basic contractile units of the fibers.

Ultrastructure of sarcomeres

Examination of sarcomeres of myofibrils by transmission electron microscopy reveals two sorts of **myofilaments**. The thicker myofilaments belong to the A band and are composed mainly of **myosin**. The thinner myofilaments are mainly found in the I band and are composed mainly of **actin**. These thin myofilaments are connected to the Z-line and partially extend between the thicker myofilaments. This area of overlap is important in the contraction process. In transverse sections in the area of overlap each thick myofilament is surrounded by six of the thinner myofilaments.

Molecular components of the myofilaments

The myofilaments are composed of four main molecules: **myosin** (thick filaments), **actin**, **tropomyosin**, and **troponin** (thin myofilaments). The actin and myosin constitute about 55% of all the proteins of the fibers.

Thin myofilaments

Two types of actin are found:

- **G-actin** (globular) consists of spherical monomers of about 5.6nm diameter. The monomers are polarized, with one hemisphere having specific binding sites for myosin.

- **F-actin** (fibrous) consists of chains or strings of G-actin molecules.

Tropomyosin is a long polypeptide molecule and to which are attached actin molecules (like a string of pearls).

Periodically **troponin** molecules are located on the tropomyosin molecules. The thin myofilaments are composed of two tropomyosin molecules with attached actin and troponin in a double helix. The troponin molecule is organized into specific regions: TnT, which binds to tropomyosin, TnC, which binds to calcium, and TnI, which in involved in inhibiting the actin-myosin interaction.

Thick myofilaments

The myosin molecules are composed of a rod-like portion (**light meromyosin**) and twin rounded heads (**heavy meromyosin**). These can be separated by brief hydrolysis. The heavy meromyosin portion contains ATP-ase activities, important in the binding of the myosin to actin during contraction process. The thick myofilaments are given structural support and held in place and by a giant

protein molecule, **titin**, which connects the myosin molecules to the Z lines. Titin extends from the Z line to the M-band approximately parallel to the long axis of the sarcomere. The part of the titin molecule in the I band extending from the Z line is known as the elastic part of the titin, whereas the part in the A band is less elastic. The most central part of the thick myofilaments are laterally connected by intermediate filaments resulting in the M-band.

The Z-lines contain the proteins α-**actinin** and **desmin**.

Contraction mechanism

The explanation for the contraction process derives from the **Sliding Interdigitating Filament Hypothesis** (of Hanson and Huxley of the early 1960's) based on the changes in sarcomere ultrastructure during contraction as seen by transmission electron microscopy. During muscle fiber contraction sarcomeres become shorter, the Z lines move closer to each other and the I bands become less prominent. The A bands remain the same length in all phases of the contraction. The changes in the length of the sarcomere are the result of the thin myofilaments sliding or interdigitating between the thicker filaments resulting in a greater area of overlap.

T-system of tubules

Tubular invaginations of the sarcolemma penetrate the myofibers in a transverse direction. These are known as **the T-tubules** (transverse tubules) and are found at the area of overlap between the A and I bands of myofibrils. Each sarcomere has two of these tubules. The **sarcoplasmic reticulum** is a network of **sarcotubules** surrounding each myofibril. Swollen **terminal cisternae** or sacs of the sarcoplasmic reticulum are associated with the T-tubules. Two terminal cisternae are associated with each T-tubule to form structures (visible by transmission electron microscopy) known as **triads**. The membranes of the terminal cisternae are separated from the T-tubules by gap junctions. These terminal cisternae are sites of accumulation of calcium ions during muscle relaxation and play an important role in the contraction process.

Mechanism of muscle contraction

- Each myofiber is innervated by efferent nerve impulses from axon terminals of motor end plates.
- The nerve impulse causes depolarization of the sarcolemma and this depolarization continues in the T-tubule.

- On reaching the triad the impulse causes the release of accumulated calcium ions from the terminal sacs of the sarcoplasmic reticulum into the sarcoplasm.
- The calcium ions unite with binding sites of troponin molecules to form a troponin-calcium complex. This results in the exposure of the active-binding sites of the G-actin allowing their interaction with the globular heads of heavy meromysosin.
- The process is energy dependent involving mitochondrial ATP and ATP-ase activity from the heavy meromysoin.
- The angle of the globular meromyosin heads changes repeatedly resulting in their binding with adjacent actin molecules in a rachet-like manner. This results in the filament sliding process and the changes seen in the sarcomeres during fiber contraction.
- At the end of contraction, the calcium ions break their connections with the troponin and accumulate again in the terminal saccules of the triads.

Imbalance in calcium ion homeostasis or a lack of ATP results in a breakdown of the contraction mechanism and may cause stable actin-myosin complexes and **tetany**. A similar muscular rigidity occurs after death (**rigor mortis**).

Other components of the sarcoplasm

- **Glycogen** particles are found and serve as energy stores. (These can be demonstrated by the PAS (periodic acid-Schiff) reaction in histological sections. At the ultrastructural level the spherical glycogen particles (β - particles) are seen individually or in small clusters).

- Many elongated **mitochondria** are found located between the myofibrils or in accumulations just under the sarcolemma. The numbers and activities of the mitochondria are greater in muscle fibers with high metabolic activity.

- **Myoglobin** is an oxygen-binding protein that gives much of the red color of muscle fibers.

- Relatively little rough endoplasmic reticulum or ribosomes are present in myofibers.

- In aged muscle fibers **lipofuscin** deposits (brown pigment) are common. These are now known to be large secondary lysosomes.

Classification of muscle fibers

Muscle fibers are classified into three main categories:

- **Red fibers (Type I) or slow-twitch high-oxidative fibers**

These have relatively small diameters, much myoglobin, many well-developed mitochondria, a rich blood supply and much ATP-ase. These type I fibers are found in muscles with very high metabolic activity involved in slow sustained contractions. The energy source is from oxidative phosphorylation.

- **White fibers (Type IIa) or fast-twitch glycolytic-anaerobic fibers**

These have larger diameters, less myoglobin and fewer mitochondria, relatively poorer blood supplies and less ATP-ase. These type IIa fibers are involved in rapid contraction (fast twitch) with anaerobic glycolysis.

- **Intermediate fibers (Type IIb)**

These have structural and functional properties in between those of the other two types.

Muscles are characterized according to the predominance of the fiber types. Red muscle ("red meat") is dominated by type I fibers. White muscle ("white meat") is dominated by type IIa fibers. Most muscles are a mosaic of all the muscle types. The gross color reflects the differing proportions of the muscle types. This mosaic of muscle fibers can be demonstrated in frozen transverse sections of muscles subjected to histochemical techniques for enzymatic activities. For example, localization of succinic dehydrogenase activities (localized in mitochondria) or ATP-ase activities, is commonly performed on muscle biopsies to determine the ratio of the various muscle types.

Repair and regeneration after injury

If muscles are used intensively, trained or exercised, they increase in mass as a result of increase in protein synthesis and sarcomere production. This results in **hypertrophy of use** ("Use it or lose it"). On the contrary, limb immobilization (e.g. in plaster casts, or as a result of inactivity due to hospitalization, or lack of gravity) causes loss of muscle mass (**disuse myopathy** or **atrophy**).

Myofibers are syncytial and post-mitotic, with very limited regenerative abilities after trauma. After trauma such as muscle crush, pathological changes occur in muscle and may lead to breakdown of myofibers and release of myoglobin, which can affect renal function and be life-threatening. In the

limited repair processes, satellite cells are activated, divide and can form new myotubes and myocytes. In some cases the satellite cells can fuse with existing fibers and contribute to the repair processes.

Atypical Striated Muscle

Some striated muscles of the body with typical histological appearance of striated muscle, are involuntary muscles. An example of such involuntary striated muscle is the cremaster muscle (near the spermatic cord).

In some cases striated muscles are not really "skeletal" as they are not attached to the skeleton (e.g. esophageal striated muscle, external urethral sphincter, external anal sphincter).

CARDIAC MUSCLE

Cardiac muscle is also striated, but differs from the striated skeletal muscle in several respects:

- The muscle **fibers branch** (bifurcate) and are arranged in series to form an anastomosing network.
- Each myocyte has one or two **central nuclei** (unlike the many peripheral nuclei of syncytia of skeletal muscle fibers).
- The fibers have more sarcoplasm.
- The mitochondria are larger and better developed.
- **All the fibers are Type I** (red fibers, with abundant myoglobin, high oxidative slow-twitch).
- **Glycogen** is more common.
- The myocytes have specialized areas of contact - the **intercalated disks**.
- **Contractions are rhythmic, spontaneous and involuntary**.

The cross striations have a similar morphology and staining characteristics to those of skeletal muscle fibers, however the contractile tissue is not organized into discrete myofibrils. At the ultrastructural level sarcomeres are found similar to those of skeletal muscle fibers. The large mitochondria are arranged in rows between the strings of sarcomeres. In histological preparations this gives the impression of longitudinal striations, though these are not myofibrils (Cardiac myocytes lack myofibrils). In aged cardiac muscle, **lipofuscin** is also commonly found.

Cardiac myocytes also possess a system of **T-tubules**. These consist of fairly broad tubular sarcoplasmic invaginations, which terminate in the region of the

Z-line of the sarcomeres. Typically these are associated with a single terminal saccule of sarcoplasmic reticulum to form **diads**. In general the sarcoplasmic reticulum of cardiac muscle fiberes is much less well developed than that of myofibers of skeletal muscle.

Intercalated disks

These are step-like areas of interdigitation between adjacent sarcomeres. At the ultrastructural level the intercalated disks are seen to have two main components:

- **transverse regions**, rich in desmosomes and tight junctions. These are important in providing good cell adhesion between adjacent myocytes.
- **longitudinal regions**, parallel to the direction of the myofilaments. These regions have many gap junctions, which are areas of low electrical resistance and permit the spread of excitation from myocyte to myocyte.

Calcium ions play important roles in the areas of intercalated disks. Isolated hearts maintained in a culture medium with reduced calcium ion levels results in a separation of myocytes at the intercalated disks.

Conducting System of the Heart

The contraction of heart muscle is involuntary. The heart has its own system for **impulse generation and conduction**.

- The **impulse generating system** consists of the Sino-Atrial Node (**SA node**), which is composed of modified muscle cells and serves as the "**pacemaker**" of the heart. This SA node is also supplied with fibers of both the sympathetic and parasympathetic nervous system. The SA node cells cause regular waves of depolarization.
- The **conducting system** consists of the Atrio-Ventricular Node (**AV node**) and **Bundle of His**. This system has modified muscle fibers called **Purkinje fibers**, which conduct the impulses. These Purkinje fibers are well seen in cardiac preparations of the endocardia of the ventricles. Each Purkinje fiber consists of rows of connected Purkinje cells. Purkinje fibers are larger than normal cardiac myofibers and each fiber possesses a large central nucleus, surrounded by perinuclear region rich in glycogen. These fibers have well-developed sarcoplasmic reticulum, and relatively little contractile material. Purkinje fibers lack T-tubules.

Cardiac muscle fibers lack motor end plates (unlike skeletal muscle fibers).

Cardiac hormones

Peptide hormones are synthesized and secreted from atrial muscle cells. The hormones are called **atrial natriuretic hormones** and are involved in the homeostasis of sodium in the body. The atrial cells that produce the hormones possess accumulations of membrane-bound storage granules visible by transmission electron microscopy.

Hypertrophy and regeneration of cardiac tissue

There is virtually no regeneration of cardiac tissue. The coronary arteries supplying blood to the heart are anatomical end arteries and lack collaterals. In the event of blockage of coronary arteries (as a result of a blood clot or atherosclerotic blockage), the cardiac myocytes vascularized by the coronaries cannot receive essential oxygen and the result is infarct. Following infarcts, the remaining heart muscle undergoes compensatory hypertrophy, with subsequent enlargement of the heart. Hypertrophied hearts are commonly an indication of underlying pathological disorders, though they may develop in specific cases of training and overload as in athletes.

SMOOTH MUSCLE

Smooth muscle is also known as "**involuntary muscle**", as contraction is not under conscious control. Smooth muscle is innervated by the **autonomic nervous system**.

Smooth muscle lacks cross-striations (unlike striated and cardiac muscle). Moreover, smooth muscle has the ability to undergo hyperplasia and hypertrophy (as in the uterus of pregnant women). Smooth muscle can also regenerate, and this is important in the repair processes of injured blood vessels.

Location of smooth muscle

- Smooth muscle is found in the **walls of the hollow internal organs** (hollow viscera), where it plays a role in maintaining the patency of the lumen. Smooth muscle forms the contractile layers of the intestinal tract, where it is important in peristaltic contractions involved in the movement of food.
- Smooth muscle is found in the **walls of the respiratory tracts**.

- Smooth muscle is present in the **walls of blood vessels** (vascular smooth muscle, especially in arterial vessels).
- Smooth muscle is found in the **dermis of the skin** (arrector pili).
- Smooth muscle is found in the eye (**iris diaphragm,** controlling the amount of light reaching the retina).
- Smooth muscle is a major component in the wall of the **uterus**.

Smooth muscle is also found in many other sites in the body

Structure of smooth muscle fibers

The smooth muscle fibers (**myocytes**) are **spindle-shaped** (fusiform).

The nucleus is in the widest part of the fiber and is elongated, typically with several nucleoli. In cross section, the nucleus will be evident only when the section cuts through the widest part of the myocyte.

The length of the myocytes is very variable in different organs. In some cases, such as in the uterus during pregnancy, the length can reach 0.5mm. Typically the length of smooth muscle in the various organs is about 0.2mm. In some cases, such as in small arterioles, the length may be only about 20μ m. In most cases the thickness of the fibers at their widest part as seen in cross section is typically about 5-10μm.

In most organs, the smooth muscle fibers are orderly arranged in layers, strips or bundles. In cross section, the smooth muscle fibers are seen to form an orderly mosaic of circles of varying diameters, with the nuclei being seen only in fibers sectioned at their widest region. After regular staining (H&E) the sarcoplasm is seen to be acidophilic (stained with eosin). In sections of most of the intestinal tract, it is possible to see the two adjacent, antagonistic bands of smooth muscle (longitudinal and transverse).

Smooth muscle sheath

Each individual fiber is surrounded by a **sheath** (secreted by the fiber itself). The sheath contains proteoglycans, that stain positively with PAS reaction. A network of **reticular fibers** (shown after silver impregnation techniques) is found in the sheath and provides mechanical support for the fibers. In addition the sheath has **collagen fibrils** and **elastin fibers**. The sheath surrounding the individual myocytes is about 40-80 nm thick, except in some locations, where the sheath is absent and the membranes (sarcolemma) of two adjacent myocytes are in contact by means of gap junctions (nexuses). These are

important as low resistance pathways permitting cooperation between the cells and in particular play a role as low resistance pathways. In a layer of smooth muscle cells, nerve stimuli only innervate a limited number of cells, but the information concerning contraction can spread rapidly via the gap junctions to all the myocytes in the layer resulting in integrated contraction.

Smooth muscle cells lack an endomysium. The sheath is not the equivalent of an endomysium as in striated muscle. The sheath lacks connective tissue cells and blood vessels.

The ultrastructure of smooth muscle cells shows that the sheath appears somewhat similar to the basal lamina of epithelial cells. The organelles are located close to the nucleus in two distinct poles. The rest of the sarcoplasm is filled with **myofilaments**, though these are not arranged in ordered sarcomeres as in striated muscle. Three types of myofilaments may be seen:

- **thin myofilaments** (5-7nm thick), which are the most common type
- **thick myofilaments** (about 16nm thick), which are less common
- **intermediate filaments** (about 10nm thick). These may be grouped as "dense bodies" and are also found in contact with the sarcolemma (attachment plaques). It is thought that these intermediate filaments provide some sort of structural support for the cells.

The contraction mechanism of smooth muscle cells is still not very clear. The actin and myosin do not appear to be regularly arranged. Myosin is present in relatively low amounts. A calcium ion target protein, calmodulin, is present. The myocytes lack a T-system, though the sarcolemma has numerous small fixed saccules, known as caveolae. These caveolae may possibly have a role analogous to that of the T-system of striated muscle.

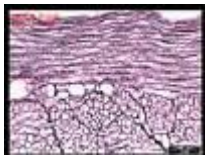
Origin of smooth muscle

Like the other muscle types, smooth muscle is also derived from **mesoderm**. Some researchers believe that smooth muscle has some affiliation to the connective tissue cells derived from mesenchyme, because the fibers synthesize and secrete collagen, elastin and reticulin of the sheath. They consider the smooth muscle fibers as connective tissue cells that have evolved the capacity of contractility.

Some glands of ectodermal origin, such as sweat glands or mammary glands, possess smooth muscle cells surrounding their secretory units (**myoepithelial cells**). These myoepithelial cells are ectodermal in origin.

Some sites of the body show an intermingling of smooth muscle fasciculi, with those of skeletal muscle (e.g. part of the esophagus, anal sphincter, tarsi of eyelids).



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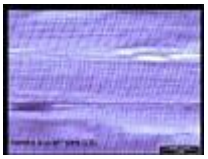
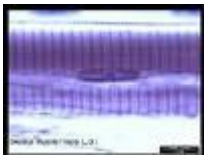
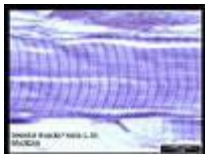
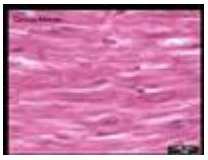
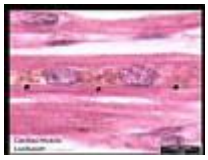




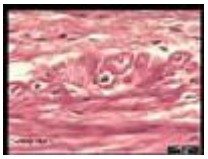
Skeletal Muscle fibers Skeletal Muscle fibers Skeletal Muscle fibers Skeletal Muscle fibers -Myofibrils



Skeletal Muscle fibers Skeletal Muscle fibers Cardiac Muscle Cardiac Muscle






Cardiac Muscle-Lipofuscin | Cardiac Muscle | Purkinje Fibers | Cardiac Muscle



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