Muscle contraction is caused by the contractile protein myosin, which exists in various isoforms (SMA and SMB) in different muscle types such as smooth, cardiac, and skeletal. Current data suggests smooth muscle myosin is in a non-functional conformation state until light chain 20, associated with the myosin head, is phosphorylated. This allows either head to freely bind to actin, a protein also involved in contraction. The contractile process is initiated with ATP hydrolysis in the ATP binding region. The release of the products from ATP hydrolysis causes the “lever arm” portion of each myosin head to bend relative to the “motor domain,” pulling the actin fibers closer together, shortening the muscle cells for movement. If the contractile process is disrupted, bodily function is impaired. These key areas were modeled by the Cudahy SMART (Students Modeling A Research Topic) team using 3D printing technology. Aortic coarctation, a developmental problem, involves a constriction of the proximal aorta, increasing blood pressure by narrowing the aorta and changing vascular smooth muscle in this region of vessel. While surgery can correct the constriction and prolong life, there remain long-term consequences, reducing life span. Drug treatments for a specific smooth muscle problem can be complicated, altering functioning of other smooth muscles, causing undesired side effects such as incontinence. The question researchers face is targeting of drugs to a specific smooth muscle tissue. Further understanding of smooth muscle function and regulation helps to better treat, prevent, and or cure this and other smooth muscle diseases.

I. Types of Muscle

Movement of the body, including internal organs and blood, is accomplished through the action of muscles. Muscle cells come in 3 varieties: skeletal, smooth, and cardiac.

Skeletal

Skeletal muscle is found attached to bones. Their primary purpose is to move the skeleton through contractions of the muscles. Structurally, skeletal muscle is striated (alternating dark and light bands) due to the organization of the thick and thin filaments. Contraction changes the relationship of these filaments, changing the striation pattern and causing shortening.

Cardiac

Cardiac muscle is located in the heart. It is responsible for causing the heart beat. Cardiac muscle cells are also striated. These cells contract in unison when they are in direct contact, generating power to pump blood.

Smooth

Smooth muscle is located in many areas of the body, including blood vessels, the digestive tract, and the bladder. Smooth muscle cells are not striated. Contraction still occurs and results in a shortening of cells. Though drastically different in appearance, all muscle cells contract to shorten lengths. The presence of the contractile protein myosin is responsible for the shortening of muscle cells. Using a second protein, actin, myosin generates a power stroke capable of contracting a cell.

II. Structural Organization of Myosin Heavy Chain

Myosin is the major contractile protein in muscle cells. Experiments have been performed to determine the structure of myosin (Figure 1: Myosin Segmentation). By identifying and understanding the structure of myosin, a clearer picture of how it functions emerges. The myosin head is the “business” end of the molecule. It hydrolyzes ATP and interacts with actin to generate force and cause shortening.

- Mornet, et al. used several different proteases to cleave the myosin head
- Results produced similar sized fragments
- Dashed lines indicated that cleavage occurred in almost same range resulting in approximate sizes 25KD, 50KD, 20KD
- Trypsin (final line) was the only area to produce different sized fragments
- Concluded there are 3 different domains in myosin heavy chain

III. Identifying Structural/Functional Domains

Each domain consists segments responsible for the overall function of the myosin. The 25KD fragment (green) includes the ATP binding site (lilac green), responsible for ATP hydrolysis. The 50KD fragment (purple) is the largest and most distal end and includes the actin binding sites (magenta and dark orchid) on either side of the binding cleft. The last COOH 20KD fragment (yellow) includes some amino acids that are close to the ATP binding site, the converter domain (red), and the lever arm (blue).

IV. Smooth Muscle Myosin Isoforms – SMA and SMB

Myosin exists in almost every cell type and in various forms. Data (Figures 2, 3, 4) help identify unique functional properties of two of the major myosin isoforms, SMA and SMB. Structurally, SMB has 7 additional residues in the ATP binding domain. It correlates with increased ATP hydrolysis, and an increased contractile velocity. With faster shortening of the cells, force generation can occur faster, allowing a faster response.

- 3 main regions (Fundus, Body, and Antrum) are divided into 10 smaller sections
- SMA and SMB content of each section was analyzed for abundance

V. Proposed Action of Smooth Muscle Myosin in Movement

Muscle movement cannot be accomplished without the interaction between myosin and actin filaments. The three types of muscle all contract using actin and myosin, however, smooth muscle myosin utilizes a different mechanism to facilitate interaction between actin and myosin. This interaction results from a variety of chemical changes. Stimulation of smooth muscle causes increased intracellular Ca2+, which activates a myosin light chain kinase (MLCK) that phosphorylates myosin light chain (MLC20), and allows myosin binding to actin and cross-bridge cycling as shown below.

(A) Myosin heads in non-conformational state
(B) MLCK phosphorylates myosin light chain 20 and myosin heads separate
(C) ADP and Pi are present in the binding domain, myosin heads bind to actin tail
(D) ADP and Pi are released, the power stroke is initiated, causing the lever arm to move the myosin head
(E) Myosin head remains bound to the actin following the power stroke
(F) ATP enters the binding domain on myosin
(G) The ATP allows it to myosin to be released from actin
ATP hydrolysis causes lever arm to return to 45° for another cycle

VI. Conclusions

Smooth muscle surrounds all hollow organs in the body, including blood vessels, airways, digestive, urinary and reproductive tracts. By understanding the processes and functions of smooth muscle myosin, scientists may be able to grasp its role in smooth muscle diseases. For example aortic coarctation (CoA) is identified by a narrowing of the proximal aorta, causing an increase in blood pressure and associated with changes in the vascular smooth muscle cells in this region of vessel. This condition is generally diagnosed early following birth. Surgery can correct the anatomical narrowing, but long term consequences that reduce overall wellness of the affected individual remain. Hypertension (high blood pressure) and ‘re-coarcting’ of the aorta are two potential outcomes that may occur later in life. Irreversible changes in smooth muscle cell function and protein expression (including SM myosin isoforms) may be responsible for the long term consequences of CoA following surgical correction. These changes may also be involved in other developmental diseases and pathological conditions. Pharmaceutical treatments for a specific smooth muscle condition pose a problem as these drugs may also alter function of other smooth muscle tissues. This inability to target specific tissues may cause undesired side effects. Researchers face the task of finding drugs that act solely on a specific smooth muscle tissue.