Regulation of Smooth Muscle Mechanical Adaptation

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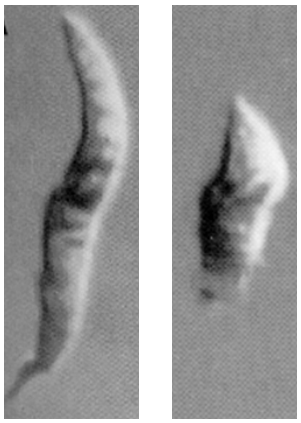
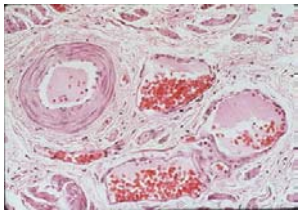
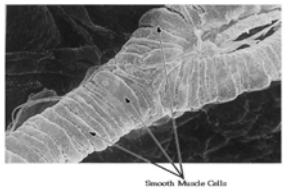
Smooth muscles are small, fusiform cells that act as linear motors to control volumes and pressures of most hollow organs of the body, including blood vessels, urinary bladder, gut and bronchioles. As such, alterations in the regulation of smooth muscle cell passive and active mechanical properties play a prominent role in many debilitating chronic disorders, such hypertension, incontinence, esophageal reflux and asthma.







Smooth muscles have much in common with the more well-known striated muscles that operate to move limbs and propel blood. Perhaps the single most important common feature is the motor permitting muscle shortening and force development, which in all muscle cells, is due to the stepping of myosin crossbridges over actin cables. However, smooth and striated muscles differ in dramatic ways. One difference little appreciated until recently is the ability of smooth muscles to adapt mechanically over short time periods. Another is the ability of most smooth muscles to contract for very long times without fatiguing. A common structural feature for both mechanical adaptation and prolonged force-maintenance is the formation of load-bearing crosslinks.

The goal of our research is to understand how the rather complex biochemical cell signaling pathways activated upon muscle stimulation regulate the mechanical activities of smooth muscles to permit short-term adaptation and prolonged force-maintenance. One project that is currently underway is designed to answer the question, Does bladder smooth muscle display strain softening? Stain softening, or the “Mullins Effect”, is a reduction in stiffness of rubbery materials after the 1st loading of a stress-strain cycle that can not be attributed to viscoelasticity. The importance of strain softening in relation to muscle function is that it is considered to be due to crosslink breakage. Thus, quantification of strain softening in smooth muscle should lead to a deeper understanding of the contribution made by crosslinks in regulation of contraction. To answer the strain softening question, we are using a computer-controlled electronic lever to drive length changes of bladder smooth muscle and record the resulting force changes. Our preliminary data show that there is a loss in energy in the 1st length-force work cycle in bladder smooth muscle that is analogous to that produced in latex, a rubbery material that displays a classic Mullins Effect. The biomechanical studies will be complemented with biochemical studies to identify the protein structures that may participate in crosslink formation in bladder smooth muscle. The significance of this work is that it will provide insights into how smooth muscle cells can adapt mechanically to various conditions, and assist in the discovery of new therapeutic agents designed to treat disorders of smooth muscle-containing organs.