Inhibitor κB Kinase
Another Node in the Cell Signaling Network Regulating Smooth Muscle Contraction

Paul H. Ratz

At a recent Grand Rounds presentation, the topic of discussion was introduced as regarding “...the most important muscle of the body that nobody knows about.” Although it is clear to clinicians and physiologists that smooth muscle controls the dimensions of nearly all hollow organs of the body, and that alterations in this control system participate in diverse and debilitating disorders such as hypertension, vasospasm, vasodilatory shock, asthma, overactive bladder, and irritable bowel syndrome, the muscle type that has garnered the majority of the limelight for generations has cross- striations.

No single reason can explain smooth muscle’s limited exposition in general textbooks to account for its apparent second-class status behind striated muscle. However, a goal of science is to clarify by reduction, whereas complexity only recently has been embraced, leading to newer disciplines, such as systems biology. Studies during the past 40 years certainly indicate that smooth muscles display astounding complexity and diversity in biomechanical behavior and in regulation of contractile protein activation. Regarding the latter, the study by Ying et al in this issue of Circulation Research has added one more kinase to a growing number of regulatory proteins known to play a role in causing smooth muscle contraction.

More than 100 years ago, Ringer showed that calcium was required for heart contraction. Calcium and the thin filament protein troponin are the central players in the regulation of striated muscle contraction, permitting active myosin from continuing through its actomyosin cross-bridge cycle. Although critical molecular details of this system remain to be clarified, and with the caveat that contractile protein calcium sensitivity can be modulated, the general scheme of a calcium–troponin switch that turns striated muscle on and off is well-accepted.

As reinforced by the clinical use of calcium channel blockers, calcium also participates in regulation of smooth muscle contraction. By the 1980s, several investigators suggested that calcium regulation of smooth muscle cross-bridges involves myosin light chain kinase (MLCK), a calcium-calmodulin–dependent enzyme that phosphorylates the 20-kDa regulatory myosin light chain (MLCp). Thus, unlike striated muscle that involves thin filament regulation of contraction, smooth muscle was described as a muscle that depends on activation of a dormant myosin state. Moreover, in addition to complex calcium signaling that alters cytosolic calcium levels, MLCK itself is regulated by multiple cell signaling systems.

Although MLCK is generally accepted as a key regulator of smooth muscle contraction, numerous studies during the past 3 decades have pointed to other systems for regulation of the degree of tension developed and borne by smooth muscle. Notably, the activity of myosin phosphatase is highly regulated by both calcium-dependent and calcium-independent mechanisms, and numerous hypotheses champion thin filament–based regulation, including alterations in cytoskeletal structures. Smooth muscle actomyosin cross-bridges not only rapidly generate tension but also hold tension. These distinct modalities, a feature of certain myosin II motors, may be differently regulated. Moreover, unlike striated muscle that is on or off, constitutive rho kinase activity seems to idle the actomyosin motor of both tonic and phasic smooth muscles, although the primary role of rho kinase may be to regulate actin polymerization. Finally, MLCp can involve more than a single phosphorylation site with physiological implications. In short, the statement that smooth muscle contraction is regulated solely by a Ca2+-dependent MLCK switch seems an incomplete depiction of this complex muscle type. However, the level of steady-state MLCp remains a strong indicator of the degree of contractile tension, at least of vascular smooth muscle.

A current view is that several kinases respond to external stimuli and internal cues to modulate the ratio of phosphorylated to total MLC by regulating the MLCκB kinase (IKK), and specifically the IKKκB catalytic isotype of this enzyme complex, which represents a novel Ca2+-independent myosin kinase that seems to act in parallel with Ca2+-dependent MLCK and possibly other kinases, are now added to this list (Figure, bold italic pathway). In a tour de force study using pharmacological probes, molecular overexpression and underexpression including a smooth muscle–specific IKKκB knockout and in vitro and in vivo studies, Ying et al provide compelling evidence supporting the hypothesis that IKKκB participates in an calcium-independent increase in MLCp. Most importantly, these investigators showed that IKKκB deficiency could lower blood pressure and could reduce the degree of contraction of arteries isolated from a vascular bed relevant to the control of blood pressure. Issues that remain to be determined should clarify the IKK-MLCp regulatory system. For example, whether IKKκB plays a role in regulation of phosphorylation of the myosin phosphatase–targeting subunit.
at threonine 853, and thus acts to inhibit myosin phosphatase activity, was not determined. Moreover, a notable feature of human vascular smooth muscle cells in culture identified by Ying et al. was that IKK2-induced MLCP reflects basal IKK2 activity, so pharmacological inhibition of IKK2 was capable of reducing MLCP induced by several diverse contractile agents. Whether constitutive IKK2 or proinflammatory stimuli play a further contribution regarding the influence of the different constituents of the blood on the contraction of the heart. J. Physiol. 1883;4:29–42.3.


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