

# Regulation of smooth muscle contraction by monomeric non-RhoA GTPases

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Smooth muscle contraction in the cardiovascular system, airways, prostate and lower urinary tract is involved in the pathophysiology of many diseases, including cardiovascular and obstructive lung disease plus lower urinary tract symptoms, which are associated with high prevalence of morbidity and mortality. This prominent clinical role of smooth muscle tone has led to the molecular mechanisms involved being subjected to extensive research. In general smooth muscle contraction is promoted by three major signalling pathways, including the monomeric GTPase RhoA pathway. However, emerging evidence suggests that monomeric GTPases other than RhoA may be involved in signal transduction in smooth muscle contraction, including Rac GTPases, cell division control protein 42 homologue, adenosine ribosylation factor 6, Ras, Rap1b and Rab GTPases. Here, we review these emerging functions of non-RhoA GTPases in smooth muscle contraction, which has now become increasingly more evident and constitutes an emerging and innovative research area of high clinical relevance.

## 1 | INTRODUCTION

Smooth muscle contraction in the cardiovascular system, airways, lower urinary tract and prostate is primarily involved in the pathophysiology of many diseases, which have a high mortality and are also causing high individual and socio-economic burden, such as in cardiovascular and obstructive lung diseases plus lower urinary tract symptoms. Accordingly, inhibition of smooth muscle contraction is an important strategy in medical treatment of these diseases, which together affecting billions of patients worldwide. In line with the prominent role of smooth muscle tone in health, disease and therapy

the molecular mechanisms of contraction and relaxation were and are the subject of continuous research.

Smooth muscle contraction is induced by receptors, by mechanical and other stimuli, which subsequently activate intracellular, contraction-mediated signalling pathways. These pro-contraction signalling pathways all end in a few final mechanisms, which are absolute prerequisites for smooth muscle contraction, including myosin light chain (MLC) phosphorylation, actin polymerization, organization and attachment of filaments to membranes and anchoring of cells to the extracellular matrix (Kim, Appel, Vetterkind, Gangopadhyay, & Morgan, 2008; Puete, Lubomirov, & Pfister, 2009). Intracellular signalling pathways resulting in contraction include calcium-dependent mechanisms that parallel increases of calcium sensitivity, which was realized early during the exploration of smooth muscle contraction. The role of the small monomeric GTPase RhoA for signal transduction promoting vascular smooth muscle contraction by immediate increases of calcium sensitivity has been recognized since 1992

**Abbreviations:** ARF, adenosine ribosylation factor; BPH, benign prostatic hyperplasia; Cdc42, cell division control protein 42 homologue; Egac, exchange protein directly activated by cAMP; GDI, guanine nucleotide dissociation inhibitor; GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factor; IP<sub>3</sub>, inositol-1,4,5-trisphosphate; MLC, myosin light chain; MLCc, myosin light chain-kinase; MYPT1, myosin targeting subunit.

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# Regulation And Contraction Of Smooth Muscle Progress In Clinical And Biological Research V245

**K. Kohama,K. Saida**



## **Regulation And Contraction Of Smooth Muscle Progress In Clinical And Biological Research V245:**

*Biological & Agricultural Index*, 1997      *Regulation and Contraction of Smooth Muscle* Marion J. Siegman, Andrew P. Somlyo, Newman L. Stephens, 1987-10-25 Spanning a broad spectrum of experimental approaches this volume explores the problem of regulation and contraction of smooth muscle at every level from the molecular to the whole tissue It offers insights into various areas of this field that are not yet fully understood such as the molecular packing of the native myosin filaments and the conformational changes of the crossbridge associated with the ATPase cycle Among other topics discussed are ultrastructure and crossbridge kinetics biochemistry of contractile and regulatory proteins pharmacological probes of regulatory systems mechanics and energetics and regulatory mechanisms in intact and skinned muscles Also highlights a number of outstanding reports including a review of the ultrastructural techniques that have enabled the visualization of crossbridges in smooth muscle in the rigor state In addition the book also reviews a major hypothesis on the role of myosin light chain phosphorylation as the key element in regulation of the contractile process by calcium      *Regulation of Smooth Muscle Contraction* Robert S. Moreland, 2012-12-06 Sixth Annual Graduate Hospital Research Symposium REGULATION OF SMOOTH MUSCLE PROGRESS IN SOLVING THE PUZZLE Every so often a scientific conference comes at a time when everyone has new and exciting information when old dogmas do not seem to be as well established and when speakers and participants alike are ready to challenge interpretations of old and new experimental data This was such a conference What turns on a smooth muscle cell The precise answer to this question has eluded scientists for much longer than I have been involved in the field We know that an increase in cytosolic calcium is necessary and we know that phosphorylation of the 20 kDa myosin light chain is an important step in the process We do not know if other processes are necessary for the initiation and maintenance of a smooth muscle contraction nor do we know if other processes modulate the regulation of contraction The goal of the symposium on which this volume is based was to explore the most current hypotheses for the answers to these questions I believe that after reading the chapters included in this volume you will agree that this goal was achieved The importance of calcium and calmodulin dependent myosin light chain phosphorylation in the regulation of smooth muscle contraction was reinforced by many presentations However the status of myosin light chain phosphorylation as a simple calcium dependent switch came under serious suspicion      *Regulation of Smooth Muscle Contraction* Robert S Moreland, 1992-01-31      *Regulation of the Contractile Cycle in Smooth Muscle* Takeshi Nakano, David J. Hartshorne, 2012-12-06 At the Mie International Symposium held in Japan in April 1994 leading scientists reviewed recent advances in the understanding of the contractile mechanism in smooth muscle The present volume collects the papers presented at the symposium summarizing the latest advances in smooth muscle function and emphasizing important components of the contraction relaxation cycle Topics include a discussion of the smooth muscle cell membrane with emphasis on its ion channels the regulation of cytosolic  $Ca^{2+}$  levels and the relationship to force in smooth muscle aspects of

the two key regulatory enzymes involved with myosin phosphorylation dephosphorylation the molecular basis for pharmacomechanical coupling in smooth muscle developments in the basic contractile mechanisms involving the crossbridge cycle of tonic and phasic muscle the role of myosin light chains and many others The approach is broad and presents contemporary opinions in pharmacology physiology and biochemistry as they relate to smooth muscle function The book will appeal not only to those working in these disciplines but to vascular clinicians obstetric gynecological physicians and gastroenterologists as well

**Regulation and Contraction of Smooth Muscle** International Union of Physiological Sciences. Satellite Conference on Smooth Muscle Contraction, Marion J. Siegelman, Andrew Paul Somlyo, Newman L.

Stephens, International Union of Physiological Sciences. Congress, 1987 Biochemistry of Smooth Muscle Contraction

Michael Barany, 1996-01-04 This valuable resource provides a systematic account of the biochemistry of smooth muscle contraction As a comprehensive guide to this rapidly growing area of research it covers the structure and characteristic properties of contractile and regulatory proteins with special emphasis on their predicted function in the live muscle Also included in this book are intermediate filament proteins and desmin and vimentin whose function in smooth muscle is unknown and several enzymes involved in the phosphorylation dephosphorylation of contractile and other proteins

Molecular and Cellular Aspects of Muscle Contraction Haruo Sugi, 2003 This volume presents the proceedings of a muscle symposium which was held as the Fourth Fujihara seminar on October 28 November 1 2002 at Hakone Japan This volume covers all fields of muscle biology from molecules to humans This book provides information about recent progress of muscle research as well as the problems that remain to be investigated This volume will stimulate muscle investigators to design and perform novel experiments to clarify the mysteries in muscle contraction *Muscle Contraction* Clive R.

Bagshaw, 2012-12-06 The student of biological science in his final years as an undergraduate and his first years as a graduate is expected to gain some familiarity with current research at the frontiers of his discipline New research work is published in a perplexing diversity of publications and is inevitably concerned with the minutiae of the subject The sheer number of research journals and papers also causes confusion and difficulties of assimilation Review articles usually presuppose a background knowledge of the field and are inevitably rather restricted in scope There is thus a need for short but authoritative introductions to those areas of modern biological research which are either not dealt with in standard introductory textbooks or are not dealt with in sufficient detail to enable the student to go on from them to read scholarly reviews with profit This series of books is designed to satisfy this need The authors have been asked to produce a brief outline of their subject assuming that their readers will have read and remembered much of a standard introductory textbook of biology This outline then sets out to provide by building on this basis the conceptual framework within which modern research work is progressing and aims to give the reader an indication of the problems both conceptual and practical which must be overcome if progress is to be maintained Molecular Control Mechanisms in Striated Muscle Contraction R.J.

Solaro, R. Moss, 2013-04-17 *Molecular Control Mechanisms in Striated Muscle Contraction* addresses the molecular mechanisms by which contraction of heart and skeletal muscles is regulated as well as the modulation of these mechanisms by important pathophysiological variables such as ionic composition of the myoplasm and phosphorylations of contractile and regulatory proteins. For the novice this volume includes chapters that summarize current understanding of excitation-contraction coupling in striated muscles as well as the compositions and structures of myofibrillar thick and thin filaments. For the expert this volume presents detailed pictures of current understanding of the mechanisms underlying the  $Ca^{2+}$  regulation of contraction in heart and skeletal muscles and discusses important directions for future investigation.

Smooth Muscle Spontaneous Activity Hikaru Hashitani, Richard J. Lang, 2019-06-10 This book presents the commonality and heterogeneity of the mechanisms underlying smooth muscle spontaneous activity in various smooth muscle organs and in addition discusses their malfunctions in disease and their potential as novel therapeutic targets. To facilitate understanding the volume is divided into five parts and covers 16 organs: airways, gastrointestinal tract, phasic muscle, tonic muscle, renal pelvis, ureter, urinary bladder, urethra, corporal tissue, prostate, uterus, oviducts, seminal vesicle, artery, vein, microvasculature, and lymphatic vessels. This structure will help readers to comprehend the most up-to-date information on the similarities and differences in the contractile mechanisms driving various smooth muscles as well as their potential manipulations in particular visceral organ pathologies. The vast advancements in gene, electrical recording, and imaging technologies in this field are also discussed with review of past achievements and consideration of likely future developments. This book will be of worldwide interest to clinicians, students, and researchers alike.

*Calcium and Contractility* A. K. Grover, E. E. Daniels, 2012-12-06 In organizing the present volume we had two intentions. The first was to present the best current understanding of the mechanisms of calcium mobilization during excitation-contraction coupling of smooth muscle at a level suited to the needs of professionals interested in smooth muscle pharmacology and pathophysiology while remaining appreciable by graduate and medical students. The second intention was to provide insight into present-day controversies as well as the latest advances achieved by researchers in this field. Thus we have thoroughly discussed both the techniques and the concepts derived from their application. An attempt has also been made here to answer a number of profoundly important questions: What are the mechanisms and agents responsible for the control of contractility? What are the accompanying changes in the state of intracellular calcium ions and the mechanisms responsible for them? How does the regulation of contractility occur directly at the level of the actomyosin activity? What role do gap junctions play in cell-to-cell coupling? What are the roles of cholinergic, adrenergic, peptidergic, and nonadrenergic noncholinergic interactions in calcium mobilization in smooth muscle? What changes occur in hypertension? The impact of these recent techniques on future research is also reflected upon.

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The Regulation of Muscle Contraction

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