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The role of STIM1 and SOCE in smooth muscle contractility

C.H. Feldman[a,b], C.A. Grotegut[c], P.B. Rosenberg[d,*]

[a] Duke University School of Medicine, Durham, NC, 27704, United States
[b] Howard Hughes Medical Research Fellowship Program, Chevy Chase, MD, 20815, United States
[c] Department of Obstetrics and Gynecology, Duke University School of Medicine, Durham, NC, 27704, United States
[d] Department of Medicine, Duke University School of Medicine, Durham, NC, 27704, United States

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ABSTRACT

Contraction is a central feature for skeletal, cardiac and smooth muscle; this unique feature is largely dependent on calcium (Ca^{2+}) signaling and therefore maintenance of internal Ca^{2+} stores. Stromal interaction molecule 1 (STIM1) is a single-pass transmembrane protein that functions as a Ca^{2+} sensor for the activation store-operated calcium channels (SOCCs) on the plasma membrane in response to depleted internal sarco(endo)plasmic (S/ER) reticulum Ca^{2+} stores. STIM1 was initially characterized in non-excitable cells; however, evidence from both animal models and human mutations suggests a role for STIM1 in modulating Ca^{2+} homeostasis in excitable tissues as well. STIM1-dependent SOCE is particularly important in tissues undergoing sustained contraction, leading us to believe STIM1 may play a role in smooth muscle contraction. To date, the role of STIM1 in smooth muscle is unknown. In this review, we provide a brief overview of the role of STIM1-dependent SOCE in striated muscle and build off that knowledge to investigate whether STIM1 contributes to smooth muscle contractility. We conclude by discussing the translational implications of targeting STIM1 in the treatment of smooth muscle disorders.

Contents

Abbreviations: Ca^{2+}, calcium; CSM, cavernous smooth muscle; CPA, cyclopiazonic acid; $[Ca^{2+}]$, icytoplasmic calcium concentration; GoF, gain of function; GI, gastrointestinal; LoF, loss of function; ROCC, sreceptor-operated calcium channels; S/ER, sarco(endo)plasmic reticulum; SCID, severe-combined immunodeficiency; STIM1, stromal interaction molecule 1; SOCC, sstore-operated calcium channels; SOCE, store-operated calcium entry; TG, thapsigargin; VSM, vascular smooth muscle; VOCC, svoltage-operated calcium channels.

* Corresponding author. Tel.: +1 919 684 1712; fax: +1 919 613 5145.
E-mail address: rosen029@mc.duke.edu (P.B. Rosenberg).

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1. Introduction

1.1. Store-operated calcium entry and STIM1

The concept of store-operated calcium entry (SOCE) was first introduced in 1986 with a series of experiments by the Putney lab suggested that depletion of internal calcium (Ca^{2+}) stores controlled the extent of Ca^{2+} influx in nonexcitable cells [1]. This mechanism of Ca^{2+} entry served as a link between extracellular Ca^{2+} and intracellular Ca^{2+} stores. When the stores were full, no Ca^{2+} influx was detected, but when the stores were emptied, Ca^{2+} entry developed. Indeed, SOCE is now recognized as a ubiquitous pathway that functions to maintain Ca^{2+} homeostasis in response to depletion of internal sarco(endo)plasmic (S/ER) Ca^{2+} stores [1,2]. Extensive research over the last decade has now defined key aspects of SOCE including a Ca^{2+} sensor for store depletion and the Ca^{2+} entry pore. Stromal interaction molecule 1 (STIM1) is a single-pass transmembrane protein that acts as a Ca^{2+} sensor by activating store-operated calcium channels (SOCCs) following S/ER Ca^{2+} store depletion [3,4]. SOCCs are highly selective Ca^{2+} channels at the plasma membrane comprised of Orai1 multimers [5,6]. In the presence of adequate S/ER Ca^{2+} stores, Ca^{2+} ions bind to an EF-hand motif in the luminal domain of STIM1 [3,4]. Depletion of S/ER Ca^{2+} stores results in STIM1 aggregation (puncta formation) and subsequent allosteric activation of SOCCs [6–8]. The function of STIM1 was initially characterized in non-excitable cells; however, evidence from animal models and human mutations suggests a role for STIM1-dependent SOCE in a variety of excitable tissues. The purpose of this review is to provide a brief overview of the role of STIM1-dependent SOCE in striated muscle and build on that knowledge to investigate the lesser known role of STIM1 and SOCE in smooth muscle contractility.

1.2. SOCE in skeletal muscle

Despite early descriptions of a non-voltage dependent Ca^{2+} entry pathway in skeletal muscle fibers, the physiologic role for SOCE in skeletal muscle had been controversial [9]. Since the identification of STIM1 and Orai1 as components of SOCE, evidence has emerged that STIM1 and Orai1 are expressed in muscle where they control SOCE in order to refill SR Ca^{2+} stores [10]. Moreover, mutations in STIM1 and Orai1 in humans and mice cause two different forms of skeletal myopathies. Loss of function mutations in Orai1 and STIM1 lead to a phenotype that includes hypotonia and muscle atrophy of slow twitch fibers [11,12]. In contrast, gain of function mutations in STIM1 and Orai1 confer constitutive Ca^{2+} entry in muscle fibers even in the absence of store depletion. These patients develop a tubular aggregate myopathy that results from the accumulation of SR membrane [13–18]. Mouse models with identical mutations in STIM1 and Orai1 strongly resemble these human myopathies. It is clear from studies using these mouse models that SOCE has prominent role in muscle performance and function. It is also evident from these studies that regulation of SOCE in skeletal muscle is critically important for muscle development and contractility.

SOCE is present in resting muscle fibers and is needed to maintain Ca^{2+} homeostasis. Loss of SOCE does not however directly impact excitation contraction coupling (ECC), the Ca^{2+} signaling process the triggers muscle contractility. Single muscle contractions remain intact for muscle fibers lacking STIM1 or Orai1 indicating Ca^{2+} release from a single membrane depolarization remains intact. In contrast, high frequency stimulation of muscle activates SOCE in order to sustain muscle contraction. It is likely that this level of stimulation is seen during muscle development and mature muscle during exercise. Development of inducible, skeletal muscle specific mouse models offers the opportunity to address remaining questions. An important observation by our group and others is that the skeletal muscle phenotype described for the STIM1 null mice is far more severe than that described for the Orai1 null mice. Indeed, blocking or deleting Orai1 channels from skeletal muscles result in a mild myopathy that involves loss of slow twitch fibers. The myopathy results from the developmental deletion of Orai1 and reduced Ca^{2+} dependent growth signaling during periods of intense neonatal muscle growth. Deletion of STIM1 from skeletal muscle leads to a reduction in muscle contractility, distorted muscle structures and a drastic reduction in survival. One reason for this difference between the Orai1 and STIM1 null phenotype is that STIM1 is a multifunction signaling scaffold that may influence target proteins beyond the well-established interaction with Orai channels. We used a phage display to screen for novel STIM1 interacting partners. We found that STIM1 interacts with phospholamban in cardiomyocytes in order to enhance Ca^{2+} store refilling by S/R Ca^{2+} ATPase (SERCA2a) [19]. These studies have opened key insight to the putative function of STIM1 in cardiac muscle. Our studies implicate STIM1 dependent Ca^{2+} signaling in cardiac pacemaking through the coordinated refilling of SR stores.

1.3. SOCE in cardiac muscle

Following the description of STIM1 in skeletal muscle, several groups proposed a similar role for SOCE in cardiac muscle [20–22] Changes in the frequency and amplitude of intracellular calcium transients are altered by neural or hormonal inputs to cardiomyocytes to modify the rate and/or the force of muscle contraction. Recent studies describe how SOCE is induced by the neural and hormonal inputs. Using gene delivery techniques and loss of function mouse models it appears that STIM1 induction and SOCE are critical for the development of heart failure [20,23]. Here, STIM1 and SOCE are induced as part of the fetal gene program that is known to be expressed in hypertrophied and the failing heart. STIM1 seems to be a primary event in this process as the transgenic overexpression in the heart leads to cardiac failure [24]. An interesting concept has emerged that although STIM1 is operational in the cardiomyocyte this action is independent of Ca^{2+} entry through Orai1 [19]. While STIM1 KO cardiomyocytes displayed altered SR Ca^{2+} signaling, we did not detect SOC currents. Rather, we found that STIM1 interacts with phospholamban to regulate Ca^{2+} refilling of SR Ca^{2+} stores. We identified the interaction of STIM1 and phospholamban in a screen using phage display. Along the same lines the Chatham laboratory has proposed that STIM1 functions to mitigate the ER stress in response to hypertrophic agonists [25]. Another possibility is that STIM1 interacts and regulates the voltage gated Ca^{2+} currents in cardiomyocytes (cav1.2). Although this interaction was mapped out in neurons and smooth muscle cells, it has been difficult to demonstrate the relevance in STIM1 mutant mice [26,27]. Separating STIM1 from SOCE is consistent with the longstanding belief that STIM1 is a multifunctional signaling scaffold for Ca^{2+} signaling. We propose that much like described for skeletal muscle, STIM1 Ca^{2+} signaling is required during fast heart rate where SOCE is needed to refill the SR Ca^{2+} stores of sinoatrial cells. It is likely that SOCE is a key component of the Ca^{2+} clock mechanism during cardiac pacemaking [28].

2. STIM1 and SOCE in smooth muscle

2.1. Overview

Smooth muscle contraction is driven predominantly by Ca^{2+} flux. Increased cytoplasmic Ca^{2+} concentrations ($[Ca^{2+}]_i$) initiate a cascade of intracellular events resulting in cross-bridge cycling and subsequent cellular contraction (reviewed by Webb et al. [29]). In