Chapter 4
Store-Operated Calcium Entry Channels:
Potential Role in Cardiac Function

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ABSTRACT

Store-operated Ca^{2+} entry (SOCE) channels mediate Ca^{2+} influx from the extracellular milieu into the cytosol to regulate a myriad of cellular functions. The Ca^{2+}-release activated Ca^{2+} current has been well characterized in non-excitable cells such as immune cells. However, the role of SOCE proteins in cardiomyocytes and cardiac function has only been recently investigated. The localized endoplasmic reticulum protein, stromal interaction molecule (STIM) and plasma membrane Ca^{2+} channels, ORAI form the minimal functional unit of SOCE. The documentation of STIM and Orai expression in cardiomyocytes has raised questions regarding their role in cardiac function. Recent evidence supports the central role of STIM and Orai in gene transcription and, subsequent phenotypic changes associated with cardiac remodeling and hypertrophy. The purpose of this chapter is to provide an overview of our current understanding of SOCE proteins and, to explore their contributions to cardiovascular function and role in cardiac disorders.

INTRODUCTION

Calcium's role as a ubiquitous intracellular messenger is demonstrated by its central role in a wide range of cellular functions from cell growth, proliferation, function and even cell death. In order to elicit to cellular response, a cell recruits various pumps, exchangers and channels to regulate the concentration of Ca^{2+} (Berridge, Bootman, & Roderick, 2003; Prakriya & Lewis, 2015; J. W. Putney, 2011). The endoplasmic reticulum/sarcoplasmic reticulum (ER/SR) act as an intracellular storage of Ca^{2+}, while plasma membrane (PM) channels regulate gating of Ca^{2+} from the extracellular space. Store operated Ca^{2+} entry (SOCE), is a major mechanism representing Ca^{2+} entry in many excitable and non-excitable cells. Since the first characterization of SOCE through electrophysiology, the two major components of the SOCE

DOI: 10.4018/978-1-5225-2092-4.ch004

process were identified; the ER/SR Ca^{2+} sensor, stromal interaction molecule (STIM) and, the plasma membrane (PM) localized Orai protein as the store-operated channels (Fahrner, Derler, Jardin, & Romanin, 2013; J. W. Putney, 2011; Shaw & Feske, 2012). Upon depletion of inositol-1, 4, 5-trisphosphate (IP_3) or Ryanodine (RyR)-sensitive ER/SR stores, localized ER sensor STIM directly couples with PM Orai channels mediating Ca^{2+} influx. Since the depletion of ER/SR Ca^{2+} is the trigger for PM Ca^{2+} entry, this pathway was appropriately named "store operated Ca^{2+} entry". SOCE-mediated Ca^{2+} entry not only allows for refilling of the ER/SR stores but also helps maintain Ca^{2+} homeostasis. The sustained entry of Ca^{2+} also serves other purposes such as activation of secretion, modulation of enzyme activation, and initiation of transcriptional signaling (J. W. Putney, 2011). Since SOCE-mediated Ca^{2+} influx is involved in vital cellular processes, it is not surprising that aberrant SOCE function has been implicated in many disease states including immunodeficiency, acute pancreatitis, Alzheimer's disease, Duchenne muscular dystrophy and cardiac hypertrophy (Karlstad, Sun, & Singh, 2012; J. W. Putney, 2011)

Since its discovery, the SOCE phenomenon has been well characterized in non-excitable immune cells (Prakriya & Lewis, 2015; Shaw & Feske, 2012). Soon after, SOCE-induced Ca^{2+} influx was shown to play a critical role in excitable cell such as neurons, skeletal muscle cells, and cardiomyocytes (Hartmann et al., 2014; Liu, Xin, Benson, Allen, & Ju, 2015; Majewski & Kuznicki, 2015; Stiber et al., 2008; Tojyo, Morita, Nezu, & Tanimura, 2014). Several studies have demonstrated the expression of STIM and Orai in adult cardiomyoctes, ventricular myocardium, and the sinoatrial node (Wolkowicz et al., 2011; Zhu-Mauldin, Marsh, Zou, Marchase, & Chatham, 2012). In fact, strong evidence suggests that the STIM1 and Orai play a key role in the progression of cardiac hypertrophy. Recent investigations have shown the increased expression of STIM1 in a hypertrophic response (Collins, Zhu-Mauldin, Marchase, & Chatham, 2013). With advances in molecular techniques and transgenic models, studies have provided insight into the role of Orai and transient receptor potential (TRP) channels in the etiology of several cardiovascular diseases (Yue et al., 2015). The goal of this chapter is to provide an overview of our current understanding of molecular regulation of SOCE and highlight the role of STIM1/Orai-1-mediated SOCE in cardiomyocyte function and pathology.

STORE OPERATED CALCIUM ENTRY

The ligation of agonists such as growth factors, neurohormonal stimuli, and inflammatory mediators to G-protein coupled receptors or receptor tyrosine kinases initiates the activation of phospholipase (PLC) enzymes. PLC hydrolyzes phosphatidylinositol 4, 5 bisphosphate into diacylglycerol and inositol 1, 4, 5-trisphosphate (IP_3). IP_3 binds to the IP_3 receptor (IP_3R) on the ER/SR, triggering Ca^{2+} release into the cytosol and mobilizing an increase in cytosolic Ca^{2+} ($[Ca^{2+}]_i$) (Berridge et al., 2003; Oh-hora & Rao, 2008). The increase in $[Ca^{2+}]_i$ can fuel activation of localized events such as calcium-induced Ca^{2+} release via the Ryanodine receptors (RyRs) or even induce downstream transcriptional events (Bers, 2008; J. W. Putney, 2011). The discovery of IP_3 led to our understanding that the consequence of IP_3 production was a transient increase in $[Ca^{2+}]_i$, followed by a sustained influx of Ca^{2+} from the extracellular space. While the increase in $[Ca^{2+}]_i$ was identified as a product of IP_3 activating the IP_3R in the ER/SR, the mechanism underlying Ca^{2+} influx remained unclear (Berridge, 1993). Several studies suggested that a PM-Ca^{2+} pathway was responsible for directly reloading the ER/SR stores. The idea of SOCE, initially described as "capacitative Ca^{2+} entry (CCE)", first described by Putney, reflected these conclusions. This model suggested that Ca^{2+} from extracellular space directly loaded the ER (the "capacitor") (J.