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ROS and Ca²⁺—Partners in sickness and in health

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1. Introduction

Cytosolic Ca²⁺ concentration ([Ca²⁺]_i) is a critical factor in the regulation of a plethora of physiological functions, including muscle contraction, secretion, metabolism, gene expression, cell survival and cell death [1–4]. Such regulation typically occurs in response to increases in [Ca²⁺]_i that are triggered by various physiological stimuli that modulate plasma membrane Ca²⁺ influx pathways or induce release of Ca²⁺ from intracellular Ca²⁺ stores, such as the ER and lysosomes. Although [Ca²⁺]_i increases are detected as a local or global signals in cells and often involve more than one type of Ca²⁺ flux mechanism, cell function is differentially and specifically regulated. There is increasing evidence that this specificity is controlled by restricted local, rather than global, changes in [Ca²⁺]_i [4,5]. Cells exert tight control of [Ca²⁺]_i by modulating activities of Ca²⁺ pumps and Ca²⁺ channels both in the plasma membrane as well as intracellular membranes [1,6]. These include ATP-dependent Ca²⁺ pumps in the plasma membrane (PMCA), the ER (SERCA) and organelles (SPCA); Ca²⁺ release channels in the ER (IP₃ and ryanodine receptors); Ca²⁺ channels in endolysosomal membranes (mucolipins and TPCs), mitochondrial Ca²⁺ uptake via MCU and recycling via NCXL; and plasma membrane Ca²⁺ entry channels (voltage dependent channels, Orai channels, as well as TRP channels). Contributions of these Ca²⁺ flux pathways shape the amplitude as well as temporal and spatial characteristics of [Ca²⁺]_i increases in cells [7,8]. Importantly, aberrant [Ca²⁺]_i signals caused by alteration in function of any of these Ca²⁺ flux mechanisms, in particular Ca²⁺ influx channels, have been linked to disease, dysfunction, and cell death [9,10].

Reactive oxygen species (ROS) are critical intracellular signaling factors that control cellular metabolism, cell proliferation, cellular migration, vascular tone, cell death and other cellular functions [11–14]. However, high ROS levels exceeding the cellular antioxidant capacity cause detrimental effects with pathological consequences [11,14]. Increasing evidence suggests a close interplay and cross-talk between Ca²⁺ and ROS signaling systems which fine tunes cellular signaling networks. However, disruption of one system can severely impact the other, triggering a cascade of signaling events that can be pathophysiological, ultimately causing dysfunction, disease, or cell death. ROS are derived from molecular oxygen by electron transfer reactions resulting in the formation of superoxide anion radical (O₂^{•−}), and subsequently hydrogen peroxide (H₂O₂), either spontaneously, or by the action of superoxide dismutases (SOD). High ROS levels in the cell can be achieved endogenously

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(e.g. in several cardiac pathologies), or exogenously (e.g. by irradiation or administration of chemotherapeutics). In the presence of iron, superoxide and H_2O_2 leads to the formation of highly reactive hydroxyl radicals, which can damage cellular proteins, RNA, DNA and lipids. Hydrogen peroxide, the product, is diffusible over membranes and therefore has been frequently considered to act as a second messenger. Interaction of ROS with nitric oxide or fatty acids can lead to the formation of reactive nitrogen species that are also highly reactive [11,12,15–18].

Interactions between ROS and Ca^{2+} signaling are bidirectional [11,12,14]. It has been well established that increases in $[\text{Ca}^{2+}]_i$ activate ROS-generating enzymes and formation of free radicals. However, ROS in turn triggers cellular signaling pathways that result in unregulated $[\text{Ca}^{2+}]_i$ signals. Such ROS effects can also include direct modification of the molecular component of Ca^{2+} transporters and channels or their regulatory components, including membrane lipids [19–22]. Aberrant cross-talk between Ca^{2+} -ROS pathways plays an essential role in many pathophysiological conditions and diseases such as Parkinson disease and Alzheimer disease, inflammatory diseases, and cancer.

This special issue of Cell Calcium entitled “**ROS in Ca^{2+} signaling and Disease**” addresses in a comprehensive way the impact of ROS on Ca^{2+} signaling, cell function, and disease. The reviews cover key areas in this topic including ROS methodologies; impact of ROS on intracellular Ca^{2+} regulation and plasma membrane Ca^{2+} channels; ROS effects on cell function in physiology and disease. Finally, several reviews discuss the mechanisms underlying ROS involvement in disease, new developments in identification of targets and novel therapy approaches. Eighteen reviews written by experts in the respective areas will be compiled into two volumes. This first volume contains reviews that discuss state-of-the-art methodologies in detection of ROS, ROS effects on intracellular Ca^{2+} and ROS effects on plasma membrane Ca^{2+} entry channels. Sections focused on ROS effects on plasma membrane Ca^{2+} channels, cell function as well as novel mechanisms and therapies will be presented in the second volume of this series.

2. Recent developments in ROS methodologies

This section includes two reviews focused on new genetically encoded sensors (GEFI) that can be used for measuring both ROS as well as Ca^{2+} . It is becoming increasingly apparent that many cellular functions are not regulated by global changes in Ca^{2+} or ROS, but by the formation of transient local microdomains of these signals or their compartmentalization in specific cellular locale [11,23–26]. The review by Gibhardt et al. [27] covers detectors for H_2O_2 , ROS as well as RNS and Ca^{2+} and discuss their applications. The review by Booth et al. focus on exciting new ways in which second messengers, interacting locally at organellar interfaces within cells can be tracked and measured, discussing recent developments in technology that allow monitoring of ROS in spatially and temporally resolved manner and even simultaneously with monitoring $[\text{Ca}^{2+}]$. The new generation of probes may be targeted to a wide range of subcellular environments, which can then provide information on local signal transduction and regulation.

3. ROS and intracellular Ca^{2+} signaling

The link between ROS and alterations in intracellular Ca^{2+} signaling is now well established. In addition to the nuclear DNA, mitochondria are major and critical target for ROS in cells [13,28–30]. Mitochondria are also key and central players in ROS-induced functional consequences in cells. Emerging areas in this field indicate that the ROS- Ca^{2+} link is bi-directional in that ROS generated in the cell can cause changes in $[\text{Ca}^{2+}]_i$ and mitochondrial $[\text{Ca}^{2+}]$ and vice versa, i.e. changes in cytosolic Ca^{2+} as well as mitochondrial Ca^{2+} lead to ROS generation. Increases in mitochondrial Ca^{2+} can occur because of increase in Ca^{2+} permeability of the plasma membrane in response to ROS, which occur by direct modification of Ca^{2+} channel proteins or in response to intermediates generated inside cells. Ca^{2+} elevation in mitochondria can generate ROS which can then diffuse out of the mitochondria, elevating cytosolic ROS [31]. Experiments using targeted chelators of free radicals such as TEMPOL, mito-TEMPO or similar agents, have been used to delineate the contributions of mitochondrial vs cytosolic ROS. Most recent models for ROS/ Ca^{2+} effects suggest a critical role for Ca^{2+} microdomains in the control of cell survival, apoptosis and autophagy following exposure to conditions that lead to an increase in ROS [23–25,30]. Such microdomains are formed by the interactions of mitochondria with intracellular membranes, such as the ER or lysosomes, which forms junctions called MAMs.

La Rovere et al. [32] present recent insights in the role of Ca^{2+} signaling in cell survival and apoptosis that is controlled by mitochondrial bioenergetics. In addition, ROS is also linked to induction of autophagy, a lysosomal process, in response to cell damage and cell stress. A role for mitochondria and ER is suggested in the latter process. Gottlieb and Bernstein [33] contribute an interesting review that discusses mitochondrial remodeling and mechanisms that govern its rearranging, recycling, and reprogramming. Mitochondria adapt to a wide range of cellular requirements, adjusting fuel utilization to meet ATP requirements and regulating ROS output. Each metabolic shift results in a corresponding shift in nuclear chromatin, epigenetic marks, the transcriptome, and ultimately, the proteome. Long-term alterations can involve mitophagy to eliminate dysfunctional mitochondria followed by biogenesis with alterations in the mitochondrial proteome. The impact of this response type in disease is discussed in this review. Mitochondria-dependent programmed cell death (PCD) in yeast shares many features with the intrinsic apoptotic pathway of mammals. With many stimuli, increased $[\text{Ca}^{2+}]_i$ and ROS generation are the triggering signals that lead to mitochondrial permeabilization and release of proapoptotic factors, which initiates yeast PCD. The potential role of the PTP in yeast PCD has generally been overlooked because yeast mitochondria lack the Ca^{2+} uniporter. Carraro and Bernardi [34] discuss Ca^{2+} and reactive oxygen species in regulation of the mitochondrial permeability transition and in programmed cell death in yeast.

The endoplasmic reticulum (ER) is a major site of Ca^{2+} storage. Ca^{2+} from ER cisternae is mainly released via the inositol 1,4,5-trisphosphate receptors (IP_3R) and ryanodine receptors (RyR). These channels are accumulated in specialized ER domains where there is association between ER and plasma membrane and ER and mitochondrial MAMs. When Ca^{2+} levels in mitochondria are high, respiratory chain activity can generate higher amounts of ROS. This ROS can target ER Ca^{2+} channels, leading to release of Ca^{2+} , further

amplifying the ROS signal. Increased ROS and Ca^{2+} load triggers opening of the PTP and release of pro-apoptotic factors. ROS interactions with Ca^{2+} channels in the ER as well as the lysosomes is discussed by Kiselyov and Muallem [35]. Lysosomes are gaining recognition as a cytoprotective organelles actively involved in limiting cellular damage. Lysosomes are involved in autophagic degradation of damaged organelles such as mitochondria, which otherwise would continue to damage the cells [36,37]. Second, lysosomes absorb transition metals from the cytoplasm, which suppresses oxidative stress. TRPML1 is an endolysosomal ion channel, permeable to mono and divalent cations including Ca^{2+} , Fe^{2+} and Zn^{2+} , which has emerged as a major regulator of the endolysosomal function [38]. Importantly, loss of TRPML1 has been linked to oxidative stress. These authors discuss the lysosomal and ER interaction with ROS in the context of disease.

4. ROS and plasma membrane Ca^{2+} entry channels

Several Ca^{2+} transporters and channels that are localized in the plasma membrane are targets of ROS, including voltage-dependent Ca^{2+} channels (VDC), members of the transient receptor potential family (TRP), and Orai channels [11,12,19,39,40]. Most TRP channels are Ca^{2+} permeable and are classified into the major subgroups; canonical TRP (TRPC1–TRPC7), vanilloid-receptor-related TRP (TRPV1–TRPV4), melastatin-related TRP (TRPM1–TRPM8), polycystins (TRPPs) and TRPNL (TRPML1–TRPML3) channels. Members of all subfamilies have been associated with redox regulation and oxidative stress. TRPM2 channel was the first identified as a ROS-sensitive TRP channel. Activation by hydrogen peroxide was suggested to be mediated by ADP-ribose (ADPR). This pathway has been related to cell death, and to chemokine production in monocytes. Ogawaa et al. [41] discuss the sensing of ROS and oxidative stress by TRP channels. They propose that TRP channels can act as biosensors and detect cellular redox status to regulate cellular signals. ROS can regulate TRP channels directly via amino acid modification or indirectly by generating second messengers. They further discuss the unique chemical properties of redox sensitive TRP channels and their physiological significance in Ca^{2+} signaling.

Sukumaran et al. [42] highlight the role of TRPC channels in modulating ER stress and autophagy. They discuss recent findings showing that the ER Ca^{2+} store is crucial in maintaining cellular homeostasis and serves as a checkpoint for opposing processes leading to cell survival or death. Ca^{2+} determines this selection by regulating autophagy role in promoting cell survival or apoptosis. Sukumatan discuss onset of autophagy in the context of ER stress, which has a role in numerous diseases. TRPC proteins integrate and relay cellular signals by mechanisms involving lipid recognition and lipid-dependent gating, which are likely to be relevant under conditions of redox imbalance. A complex interplay of protein–protein and protein–lipid interactions is likely to govern the gating and/or plasma membrane recruitment of TRPC channels. Svobodova and Groschner [43] provide an update on the current understanding of the lipid-dependent control of TRPC channels with focus on the TRPC lipid sensing, signal-integration hub and a short discussion of potential links to redox signaling. The review by Bhardwaj et al. [44] addresses Redox modulation of channels formed by the assembly of Orai1 and STIM1. STIM1 and Orai1 constitute the core of store-operated Ca^{2+} entry pathway and loss of function of these proteins is associated with severe

immune, neuronal, GI and muscular disorders [45]. The STIMs are ER- Ca^{2+} sensors that respond to the ER Ca^{2+} depletion and translocate to the ER/PM junctions where they interact with and gate plasma membrane channels such as Orai1 and TRPC channels [46]. STIMs and Orai1 are exposed to oxidative modifications in the ER, the cytosol, and at the cell surface, and redox-mediated alterations in STIM1/Orai1 coupling can contribute to autoimmune disorders and cancer progression. The review by Bhardwaj et al. discusses the redox reactivity of cysteine residues in STIMs and Orais isoforms, focusing on the oxidative modifications of STIMs and Orais proteins that modulate their function.

5. Concluding remarks

Ca^{2+} signaling is a ubiquitous mechanism that underlies the regulation of cell function. The indispensable role of Ca^{2+} in physiology has been recognized since the time of Ringer studies [47]. Recent studies have advanced the field providing new methodologies that have allowed assessment of Ca^{2+} signaling events at a subcellular level. These studies reveal complex interaction between organelles that modulate the temporal and spatial characteristics of Ca^{2+} signals. The location and pattern of a Ca^{2+} signal is key to the cellular consequences. Cells tightly regulate Ca^{2+} signaling and mechanisms that generate the signals. Disruption of these mechanisms and regulatory components can cause aberrant Ca^{2+} signals that are deleterious to cells. Among factors that can cause such disruption are reactive oxygen species, ROS. ROS affect almost all aspects of Ca^{2+} signaling targeting the ER, cytosol, nucleus, mitochondria, lysosomes, and the plasma membrane. While cells have the ability to clear low levels of ROS that are beneficial to cells, by regulating metabolism, high levels of ROS cannot be handled by the cells. These lead to the generation of H_2O_2 and other reactive species, such as RNS. The aberrant Ca^{2+} homeostasis is a result of altered Ca^{2+} handling in many cellular areas, some of which affect cellular ATP generation and trigger factors that lead to cell death. However, Ca^{2+} often functions communicate with a number of other systems and pathways. ROS and Ca^{2+} also initiate autophagy that allows cells to survive under conditions of stress. Interactions among ROS and Ca^{2+} signaling can be considered as bidirectional, wherein ROS can regulate cellular Ca^{2+} signaling, while Ca^{2+} signaling is essential for ROS production.

The interplay of ROS and Ca^{2+} impact not only physiology but also pathology and disease and serve as a checkpoint between cell survival and cell death during conditions of stress. The chapters in this volume delve into the highly relevant, albeit damaging in some circumstances, partnership that exists between ROS and Ca^{2+} . The two intracellular messengers work in tandem, and sometimes in an opposing way, to regulate physiological function, sense ROS, and trigger responses that control cell fate. Improved understanding of the mechanism that fine tune the levels of ROS and Ca^{2+} within the different cellular organelles could result in novel therapeutic strategies for various diseases affected by dysfunction of the Ca^{2+} /ROS balance.

References

1. Berridge MJ, Lipp P, Bootman MD. The versatility and universality of calcium signalling. *Nat. Rev. Mol. Cell Biol.* 2000; 1:11–21. [PubMed: 11413485]

2. Zhivotovsky B, Orrenius S. Calcium and cell death mechanisms: a perspective from the cell death community. *Cell Calcium*. 2011; 50:211–221. [PubMed: 21459443]
3. Berridge MJ. Calcium signalling remodelling and disease. *Biochem. Soc. Trans.* 2012; 40:297–309. [PubMed: 22435804]
4. Berridge MJ. Calcium microdomains: organization and function. *Cell Calcium*. 2006; 40:405–412. [PubMed: 17030366]
5. Petersen OH. Ca(2)(+) signalling in the endoplasmic reticulum/secretory granule microdomain. *Cell Calcium*. 2015; 58:397–404. [PubMed: 25662795]
6. Kiselyov KK, Ahuja M, Rybalchenko V, Patel S, Muallem S. The intracellular Ca(2)(+) channels of membrane traffic. *Channels (Austin)*. 2012; 6:344–351. [PubMed: 22907062]
7. Laude AJ, Simpson AW. Compartmentalized signalling: Ca²⁺ compartments, microdomains and the many facets of Ca²⁺ signalling. *FEBS J.* 2009; 276:1800–1816. [PubMed: 19243429]
8. Putney JW, Bird GS. Calcium signaling in lacrimal glands. *Cell Calcium*. 2014; 55:290–296. [PubMed: 24507443]
9. Missiaen L, Robberecht W, van den Bosch L, Callewaert G, Parys JB, Wuytack F, Raeymaekers L, Nilius B, Eggermont J, De Smedt H. Abnormal intracellular Ca(2+) homeostasis and disease. *Cell Calcium*. 2000; 28:1–21. [PubMed: 10942700]
10. Petersen OH, Tepikin AV, Gerasimenko JV, Gerasimenko OV, Sutton R, Criddle DN. Fatty acids, alcohol and fatty acid ethyl esters: toxic Ca²⁺ signal generation and pancreatitis. *Cell Calcium*. 2009; 45:634–642. [PubMed: 19327825]
11. Gorlach A, Bertram K, Hudcova S, Krizanov O. Calcium and ROS: a mutual interplay. *Redox Biol.* 2015; 6:260–271. [PubMed: 26296072]
12. Trebak M, Ginnan R, Singer HA, Jourdain D. Interplay between calcium and reactive oxygen/nitrogen species: an essential paradigm for vascular smooth muscle signaling. *Antioxid. Redox Signal.* 2010; 12:657–674. [PubMed: 19719386]
13. Sena LA, Chandel NS. Physiological roles of mitochondrial reactive oxygen species. *Mol. Cell.* 2012; 48:158–167. [PubMed: 23102266]
14. Holmstrom KM, Finkel T. Cellular mechanisms and physiological consequences of redox-dependent signalling. *Nat. Rev. Mol. Cell Biol.* 2014; 15:411–421. [PubMed: 24854789]
15. Banfi B, Tirone F, Durussel I, Knisz J, Moskwa P, Molnar GZ, Krause KH, Cox JA. Mechanism of Ca²⁺ activation of the NADPH oxidase 5 (NOX5). *J. Biol. Chem.* 2004; 279:18583–18591. [PubMed: 14982937]
16. Murphy MP. How mitochondria produce reactive oxygen species. *Biochem. J.* 2009; 417:1–13. [PubMed: 19061483]
17. Brand MD. The sites and topology of mitochondrial superoxide production. *Exp. Gerontol.* 2010; 45:466–472. [PubMed: 20064600]
18. Mignolet-Spruyt L, Xu E, Idanheimo N, Hoeberichts FA, Muhlenbock P, Brosche M, Van Breusegem F, Kangasjarvi J. Spreading the news: subcellular and organellar reactive oxygen species production and signalling. *J. Exp. Bot.* 2016; 67:3831–3844. [PubMed: 26976816]
19. Takahashi N, Mori Y. TRP channels as sensors and signal integrators of redox status changes. *Front. Pharmacol.* 2011; 2:58. [PubMed: 22016736]
20. Bansaghi S, Golenar T, Madesh M, Csordas G, RamachandraRao S, Sharma K, Yule DI, Joseph SK, Hajnoczky G. Isoform- and species-specific control of inositol 1,4,5-trisphosphate (IP₃) receptors by reactive oxygen species. *J. Biol. Chem.* 2014; 289:8170–8181. [PubMed: 24469450]
21. Aracena-Parks P, Goonasekera SA, Gilman CP, Dirksen RT, Hidalgo C, Hamilton SL. Identification of cysteines involved in *S*-nitrosylation, *S*-glutathionylation, and oxidation to disulfides in ryanodine receptor type 1. *J. Biol. Chem.* 2006; 281:40354–40368. [PubMed: 17071618]
22. Kim HJ, Ha S, Lee HY, Lee KJ. ROSics: chemistry and proteomics of cysteine modifications in redox biology. *Mass Spectrom. Rev.* 2015; 34:184–208. [PubMed: 24916017]
23. Raturi A, Simmen T. Where the endoplasmic reticulum and the mitochondrion tie the knot: the mitochondria-associated membrane (MAM). *Biochim. Biophys. Acta.* 2013; 1833:213–224. [PubMed: 22575682]

24. Naon D, Scorrano L. At the right distance: ER-mitochondria juxtaposition in cell life and death. *Biochim. Biophys. Acta*. 2014; 1843:2184–2194. [PubMed: 24875902]
25. Murphy MP. Mitochondrial dysfunction indirectly elevates ROS production by the endoplasmic reticulum. *Cell Metab*. 2013; 18:145–146. [PubMed: 23931748]
26. Cao X, Choi S, Maleth JJ, Park S, Ahuja M, Muallem S. The ER/PM microdomain PI(4,5)P(2) and the regulation of STIM1-Orai1 channel function. *Cell Calcium*. 2015; 58:342–348. [PubMed: 25843208]
27. GIBHARDT, CS., ZIMMERMANN, KM., ZHANG, X., BELOUSOV, VV., BOGESKI, I. Imaging calcium and redox signals using genetically encoded fluorescent indicators. *Cell Calcium*. 2016. <http://dx.doi.org/10.1016/j.ceca.2016.04.008>
28. Camello-Almaraz C, Gomez-Pinilla PJ, Pozo MJ, Camello PJ. Mitochondrial reactive oxygen species and Ca²⁺ signaling. *Am. J. Physiol. Cell Physiol*. 2006; 291:C1082–C1088. [PubMed: 16760264]
29. Collins Y, Chouchani ET, James AM, Menger KE, Cocheme HM, Murphy MP. Mitochondrial redox signalling at a glance. *J. Cell Sci*. 2012; 125:801–806. [PubMed: 22448036]
30. Rizzuto R, De Stefani D, Raffaello A, Mammucari C. Mitochondria as sensors and regulators of calcium signalling. *Nat. Rev. Mol. Cell Biol*. 2012; 13:566–578. [PubMed: 22850819]
31. Li X, Fang P, Mai J, Choi ET, Wang H, Yang XF. Targeting mitochondrial reactive oxygen species as novel therapy for inflammatory diseases and cancers. *J. Hematol. Oncol*. 2013; 6:19. [PubMed: 23442817]
32. La Rovere, RM., Roest, G., Bultynck, G., Parys, JB. Intracellular Ca²⁺ signaling and Ca²⁺ microdomains in the control of cell survival, apoptosis and autophagy. *Cell Calcium*. 2016. <http://dx.doi.org/10.1016/j.ceca.2016.04.005>
33. Gottlieb, RA., Bernstein, D. Mitochondrial remodeling: rearranging, recycling, and reprogramming. *Cell Calcium*. 2016. <http://dx.doi.org/10.1016/j.ceca.2016.04.006>
34. Carraro, M., Bernardi, P. Calcium and reactive oxygen species in regulation of the mitochondrial permeability transition and of programmed cell death in yeast. *Cell Calcium*. 2016. <http://dx.doi.org/10.1016/j.ceca.2016.03.005>
35. Kiselyov, K., Muallem, S. ROS and intracellular ion channels. *Cell Calcium*. 2016. <http://dx.doi.org/10.1016/j.ceca.2016.03.004>
36. Yao Z, Klionsky DJ. The symphony of autophagy and calcium signaling. *Autophagy*. 2015; 11:973–974. [PubMed: 26046237]
37. Ghislat G, Knecht E. Ca²⁺-sensor proteins in the autophagic and endocytic traffic. *Curr. Protein Pept. Sci*. 2013; 14:97–110. [PubMed: 23305313]
38. Kiselyov K, Colletti GA, Terwilliger A, Ketchum K, Lyons CW, Quinn J, Muallem S. TRPML: transporters of metals in lysosomes essential for cell survival? *Cell Calcium*. 2011; 50:288–294. [PubMed: 21621258]
39. Bogeski I, Kummerow C, Al-Ansary D, Schwarz EC, Koehler R, Kozai D, Takahashi N, Peinelt C, Griesemer D, Bozem M, Mori Y, Hoth M, Niemeyer BA. Differential redox regulation of Orai ion channels: a mechanism to tune cellular calcium signaling. *Sci. Signal*. 2010; 3:ra24. [PubMed: 20354224]
40. Dietrich A, Chubanov V, Kalwa H, Rost BR, Gudermann T. Cation channels of the transient receptor potential superfamily: their role in physiological and pathophysiological processes of smooth muscle cells. *Pharmacol. Ther*. 2006; 112:744–760. [PubMed: 16842858]
41. Ogawa, N., Kurokawa, T., Mori, Y. Sensing of redox status by TRP channels. *Cell Calcium*. 2016. <http://dx.doi.org/10.1016/j.ceca.2016.02.009>
42. Sukumaran, P., Schaar, A., Sun, Y., Singh, BB. Functional role of TRP channels in modulating ER stress and Autophagy. *Cell Calcium*. 2016. <http://dx.doi.org/10.1016/j.ceca.2016.02.012>
43. Svobodova B, Groschner K. Mechanisms of lipid regulation and lipid gating in TRPC channels. *Cell Calcium*. 2016; 59:271–279. [PubMed: 27125985]
44. Bhardwaj, R., Hediger, MA., Demareux, N. Redox modulation of STIM-ORAI signaling. *Cell Calcium*. 2016. <http://dx.doi.org/10.1016/j.ceca.2016.03.00>
45. Lacruz RS, Feske S. Diseases caused by mutations in ORAI1 and STIM1. *Ann. N. Y. Acad. Sci*. 2015; 1356:45–79. [PubMed: 26469693]

46. Shin DM, Son A, Park S, Kim MS, Ahuja M, Muallem S. The TRPCs, orais and STIMs in ER/PM junctions. *Adv. Exp. Med. Biol.* 2016; 898:47–66. [PubMed: 27161224]
47. Ringer S, Buxton DW. Concerning the action of small quantities of calcium, sodium, and potassium salts upon the vitality and function of contractile tissue and the cuticular cells of fishes. *J. Physiol.* 1885; 6:154–161.