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How to cite

NUNES-HASLER, Paula, DEMAUREX, Nicolas. Redox regulation of Store Operated Ca^{2+} Entry. In: Antioxidants & redox signaling, 2014, vol. 21, n° 6, p. 915–932. doi: 10.1089/ars.2013.5615

This publication URL: https://archive-ouverte.unige.ch/unige:32346
Publication DOI: 10.1089/ars.2013.5615

ANTIOXIDANTS & REDOX SIGNALING
Volume 21, Number 6, 2014

DOI: 10.1089/ars.2013.5615

Discoveries

FORUM REVIEW ARTICLE

Redox Regulation of Store-Operated Ca^{2+} Entry

Paula Nunes and Nicolas Demaurex

Abstract

Significance: Store-operated Ca^{2+} entry (SOCE) is a ubiquitous Ca^{2+} signaling mechanism triggered by Ca^{2+} depletion of the endoplasmic reticulum (ER) and by a variety of cellular stresses. Reactive oxygen species (ROS) are often concomitantly produced in response to these stresses, however, the relationship between redox signaling and SOCE is not completely understood. Various cardiovascular, neurological, and immune diseases are associated with alterations in both Ca^{2+} signaling and ROS production, and thus understanding this relationship has therapeutic implications. ***Recent Advances:*** Several reactive cysteine modifications in stromal interaction molecule (STIM) and Orai proteins comprising the core SOCE machinery were recently shown to modulate SOCE in a redox-dependent manner. Moreover, STIM1 and Orai1 expression levels may reciprocally regulate and be affected by responses to oxidative stress. ER proteins involved in oxidative protein folding have gained increased recognition as important sources of ROS, and the recent discovery of their accumulation in contact sites between the ER and mitochondria provides a further link between ROS production and intracellular Ca^{2+} handling. ***Critical Issues and Future Directions:*** Future research should aim to establish the complete set of SOCE controlling molecules, to determine their redox-sensitive residues, and to understand how intracellular Ca^{2+} stores dynamically respond to different types of stress. Mapping the precise nature and functional consequence of key redox-sensitive components of the pre- and post-translational control of SOCE machinery and of proteins regulating ER calcium content will be pivotal in advancing our understanding of the complex cross-talk between redox and Ca^{2+} signaling. *Antioxid. Redox Signal.* 21, 915–932.

Introduction

Elevations in intracellular Ca^{2+} concentration control numerous specialized functions such as muscle contraction and hormone secretion, and fundamental cellular processes such as cell proliferation, migration, and apoptosis. The specificity of the cellular responses triggered by the ubiquitous Ca^{2+} ions is encoded in the spatiotemporal pattern of the Ca^{2+} elevations, whose unitary events are Ca^{2+} microdomains generated by the opening of Ca^{2+} influx channels on the plasma membrane (PM) or of Ca^{2+} release channels on the endoplasmic reticulum (ER), the main Ca^{2+} storage organelle of cells (10, 144). Local Ca^{2+} gradients are maintained around Ca^{2+} entry or Ca^{2+} release sites by the high concentration of cytosolic Ca^{2+}-binding proteins that prevent the rapid diffusion of Ca^{2+} ions within the cytosol, by the active extrusion and sequestration of the incoming Ca^{2+} ions by PM Ca^{2+} ATPases (PMCA) and SR/ER Ca^{2+} ATPases (SERCA), and by Ca^{2+} sequestration by neighboring mitochondria (166, 174). The spatial coordination of Ca^{2+} microdomains largely relies on the generation of membrane contact sites between the ER and the PM and between the ER and mitochondria, which act as intracellular signaling platforms to ensure the coordinated activities of Ca^{2+} channels, pumps, and exchangers while favoring the spatial confinement of Ca^{2+} signals (24, 77). A precise spatial control of intracellular reactive oxygen species (ROS) generation may also be important for cellular functions because appropriate concentrations of ROS are required at specific cellular locations to control processes such as protein folding within the ER and bacterial killing within phagosomes. The regulation of Ca^{2+} signals and of ROS production are tightly linked, because Ca^{2+} elevations directly and indirectly boost endogenous ROS production while ROS positively or negatively modulate the activity of all known Ca^{2+}-handling proteins, thereby affecting Ca^{2+} signals. Furthermore, ROS producing systems are

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enriched at ER-mitochondria membrane contact sites, which control the spatial coordination of Ca^{2+} signals within cells. Alterations in the functionally important Ca^{2+} and ROS signals occurring within these specialized cellular domains therefore have important impact on cellular functions, as highlighted by the severe cardiovascular, neurological, and immune diseases associated with aberrant Ca^{2+} signals or ROS production (11, 12, 25, 58).

Ca^{2+} Signaling and Store-Operated Entry

The major components of the "Ca^{2+} signaling toolkit" are illustrated in Figure 1. Pumps and exchangers (PMCA, sodium-calcium exchanger [NCX]) extrude Ca^{2+} ions across the PM or sequester them in intracellular stores (SERCA). This energy-consuming activity maintains cytosolic Ca^{2+} levels in the low nanomolar range and ensures that the ER Ca^{2+} concentration is kept around 400–1000 μM, a high concentration required for proper protein folding within the ER (126). Decreases in the ER Ca^{2+} concentration trigger the unfolded protein response and several Ca^{2+}-binding proteins residing within the lumen of the ER, notably the highly expressed chaperones calreticulin and BiP/Grp78, help maintain high resting Ca^{2+} levels by sequestering Ca^{2+} ions (34). Ca^{2+} constitutively leaks out of the ER *via* Sec61 translocon complexes (60, 103) and possibly presenilins (187), although the latter is controversial

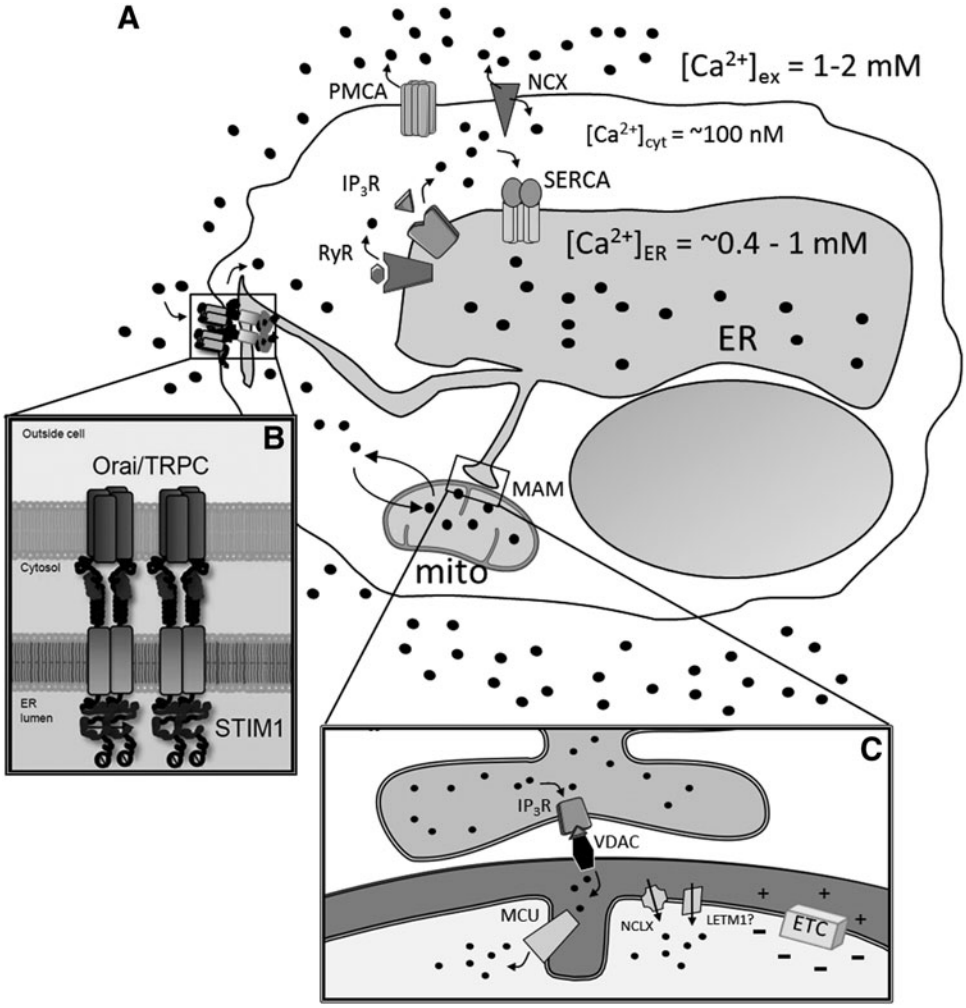

FIG. 1. Store-operated Ca^{2+} entry (SOCE). (A) Cytosolic Ca^{2+} is kept at low (nanomolar) levels in the cytosol (cyt) as Ca^{2+} is extruded from cells by the plasma membrane calcium ATPase (PMCA) and sodium-calcium exchanger (NCX), and sequestered into the endoplasmic reticulum (ER) by sarcoendoplasmic reticulum calcium ATPase (SERCA) pumps. SOCE is initiated when Ca^{2+} is released from the ER, such as upon activation of inositol 1,4,5 triphosphate receptors (IP_3R) or ryanodine receptors (RyR). The SOCE sensor stromal interaction molecule 1 (STIM1) is activated by low luminal ER Ca^{2+}, translocating to and driving the formation of tight ER-plasma membrane junctions, where it **(B)** directly gates SOC channels of the Orai or transient receptor potential, canonical (TRPC) families. **(C)** Ca^{2+} is also sequestered into the matrix of mitochondria (mito) through the low affinity, high capacity uniporter, mitochondrial Ca^{2+} uniporter (MCU), driven by the membrane potential generated by the electron transport chain (ETC), while the Na^+/Ca^{2+} exchanger NCLX subsequently extrudes Ca^{2+} from mitochondria. Mitochondria contribute to the regulation of SOCE both by buffering cytosolic Ca^{2+} and by subsequently recycling Ca^{2+} ions to sustain the refilling of the ER. The transfer of Ca^{2+} from the ER to the mitochondrial matrix is facilitated by IP_3R coupling to voltage-dependent anion channels (VDAC) at mitochondria-ER junctions termed mitochondria-associated membranes (MAMs). Please see also abbreviations list.

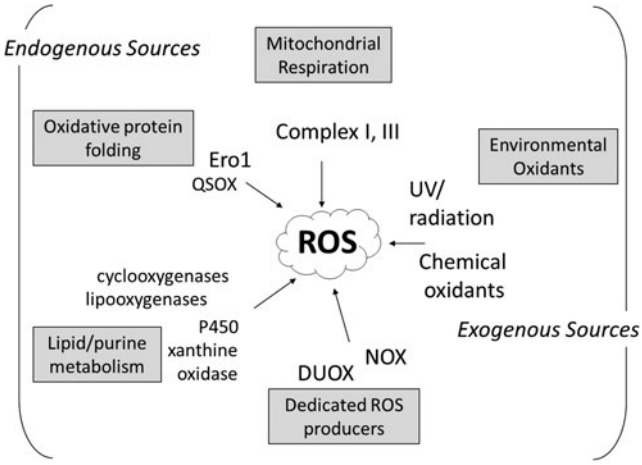

FIG. 2. Reactive oxygen species (ROS) sources. ROS may be generated from a variety of endogenous or exogenous sources. Prominent intracellular/autocrine or paracrine sources include complex I and III of the mitochondrial transport chain; ER-resident oxidoreductases Ero1 and quiescin-sulfhydryl oxidase (QSOX) responsible for driving oxidative protein folding; metabolic enzymes such as cyclooxygenases, lipooxygenases, cytochrome P450, and xanthine oxidase; and enzymes dedicated to ROS generation such as those of the NADPH oxidases (NOX) and dual oxidases (DUOX) families. Environmental chemical oxidants or ionizing radiation may also generate cellular ROS.

(181). Consequently, SERCA pumps must continuously operate to maintain ER Ca^{2+} levels and their inhibition with either the irreversible inhibitor thapsigargin or the reversible inhibitors cyclopiazonic acid and 1,4-dihydroxy-2,5-di-*tert*-butylbenzene will empty ER Ca^{2+} stores within $\sim$10 min.

The steep concentration gradient maintained by SERCA allows the explosive release of Ca^{2+} from the ER *via* the rapid opening of the inositol 1,4,5 triphosphate receptor (IP_3R) and ryanodine receptor (RyR) ligand-gated Ca^{2+} release channels (124, 128). Three IP_3R isoforms exist in mammals (IP_3R1, 2, and 3), which are ubiquitously expressed, although in varying levels depending on cell type (79, 128). They are activated by IP_3 molecules released from phosphoinositides through the action of phospholipase C in response to receptor activation, and by calcium itself. Similarly, three RyR isoforms have been identified, and they are primarily expressed in muscles and neurons, although they can be expressed in other cell types. In excitable cells, RyR are activated by calcium, often originating from the opening of PM voltage-gated channels such as the dihydropyridine receptor, which are directly apposed to RyR in tight junctions formed between the sarcoendoplasmic reticulum and the PM termed dyads and triads. Depending on cell type, membrane depolarization itself and cyclic-ADP-ribose may also activate RyR (124). IP_3R and RyR are the major Ca^{2+} release channels that mediate the regulated release of Ca^{2+} from the ER, but an as yet-unidentified receptor for sphingosine 1 phosphate can also contribute to ER Ca^{2+} release (120) and two pore channels can mediate NAADP-induced release of Ca^{2+} from lysosomes (22, 33). Release of Ca^{2+} from the ER triggers the process of store-operated calcium entry (SOCE, also called capacitive calcium entry) a ubiquitous mechanism whose main molecular components comprise the ER-resident transmembrane Ca^{2+} sensing protein stromal interaction molecule 1 (STIM1) discovered in 2005 (110, 168, 217) and the PM Ca^{2+}-selective channel Orai, also known as Ca^{2+} release-activated Ca^{2+} channel (CRAC) modulator discovered 1 year later (57, 198, 216), and subsequently shown to be the pore-forming subunit of the CRAC channel (155, 197, 207, 219). SOCE is initiated when low ER Ca^{2+} levels are sensed by STIM1 *via* its luminal Ca^{2+}-binding EF hand domains, with the unbinding of Ca^{2+} from STIM1 leading to the oligomerization and activation of STIM proteins (185, 186, 218), which then translocate to and expand membrane contact sites between the ER and the PM (114, 115, 180, 203) by a process that is not completely understood. At these contact sites the ER and PM membranes are only 10–30 nm apart (116, 141, 203) and a basic activating domain within the C-terminus of STIM proteins exposed by an intramolecular switch can electrostatically interact with an acidic domain within the cytosolic tail of Orai to trigger channel opening (36, 98, 134, 147, 209). STIM1 can also bind to and activate members of the more promiscuous cation channels transient receptor potential, canonical (TRPC) family to trigger Ca^{2+} influx (86, 210), in both cases generating cytosolic Ca^{2+} increases and promoting the refilling of the ER stores, which together are required to terminate SOCE by promoting CRAC channel inactivation (48, 85, 105) and the dissociation of STIM1-Orai1 clusters (179).

Mitochondria are an integral part of the Ca^{2+}-handling machinery *via* their ability to take up and subsequently release Ca^{2+} ions at Ca^{2+} microdomains forming near Ca^{2+} entry or release channels (164). Mitochondrial Ca^{2+} uptake is mediated by the low-affinity mitochondrial Ca^{2+} uniporter (MCU) (8, 43) whose activity requires high Ca^{2+} concentrations only reached at contact sites between mitochondria and Ca^{2+} entry or release channels (163). Efflux of Ca^{2+} from mitochondria occurs across the Na^+-Ca^{2+} exchanger NCLX, which drives the slow extrusion of Ca^{2+} in exchange for sodium (142) and possibly across the Ca^{2+}-H^+ exchanger Letm1 (90), reviewed in (170). Ca^{2+} uptake by mitochondria shapes the spatiotemporal patterns of cellular Ca^{2+} signals, thereby modulating the activity of pumps, channels, and exchangers on nearby membranes (47, 61, 131, 151). The rapid uptake of Ca^{2+} by mitochondria regulates the activity of Ca^{2+} release and entry channels (84), whereas the subsequent slow release of the captured Ca^{2+} ions fuels the activity of nearby SERCA to promote the Ca^{2+} refilling of the ER (5, 62). Early electrophysiological recordings revealed that mitochondria sustain the activity of SOCE channels by preventing their slow Ca^{2+}-dependent inactivation (84, 220), an intrinsic negative feedback mechanism that limits the amplitude of SOCE-mediated Ca^{2+} influx during cell activation (146). While fast (10–100 ms) Ca^{2+}-dependent inactivation is mediated by interactions between STIM1 modulatory domain and Orai1 intracellular loop (48), the slow (10–100 s) Ca^{2+}-dependent inactivation is thought to involve Ca^{2+} sequestration by mitochondria of the Ca^{2+} ions entering across SOCE channels (65, 84). Such modulation implies a close apposition between mitochondria and SOCE channels as Ca^{2+}-dependent inactivation is spatially restricted and mitochondrial Ca^{2+} uptake only occurs at high Ca^{2+} microdomains (163). However, recent morphological and functional studies indicate that subplasmalemmal mitochondria are not exposed to high Ca^{2+} concentrations during SOCE (64) and that mitochondria do not directly interact with SOCE channels activated by STIM1 at ER-PM contact sites (98). These

findings challenge the paradigm that mitochondrial regulation of SOCE channel inactivation involves Ca^{2+} buffering and suggest that other mechanisms might mediate the mitochondrial modulation of SOCE channel gating. Deciphering the precise nature of these mechanisms will be critical to gain a complete understanding of the relationship between mitochondrial Ca^{2+} fluxes and SOCE.

While mitochondrial Ca^{2+} uptake shapes Ca^{2+} signals, the ensuing elevations in mitochondrial matrix Ca^{2+} increase the activity of dehydrogenases of the citric acid cycle to boost cell metabolism to match the increased energy demand (74). In addition, Ca^{2+} signals dynamically regulate the mitochondrial proton gradient (152), an important bioenergetic parameter that drives the electroneutral fluxes of substrates, metabolites, and ions required for mitochondrial respiration and volume homeostasis (150). The transfer of Ca^{2+} between the ER and mitochondria occurs at membrane contact sites known as mitochondria-associated ER membranes (MAMs), a subdomain of the ER with distinct biochemical properties linked to mitochondria by protein tethers (24, 77, 164). In yeast, members of ER-Mitochondria Encounter Structure (ERMES) complex act as tethers and mediate the interorganellar interaction (77, 97). Although no clear ERMES homologs have yet been identified in mammals, MAM-resident IP_3R interacts with the mitochondrial anion channel voltage-dependent anion channel (VDAC) through the cytosolic chaperone Grp75 (157, 163, 188). Other ER-mitochondrial interacting pairs include ER-residing mitofusin-2 forming homo- and heterologous complexes with mitochondrial mitofusin-2 and mitofusin-1 (42); the ER protein VAPB and mitochondrial PTPIP51 (44); and ER transmembrane apoptosis factor Bap31 and mitochondrial fusion protein Fis1 (88). In addition to their specific signaling functions, these tethers maintain mitochondria 10–30 nm apart from ER subdomains enriched in IP_3R, SERCA, and in the Ca^{2+}-binding proteins calnexin and calreticulin (136, 182), enabling the quasi-synaptic transfer of Ca^{2+} from the ER to mitochondria to control oxidative phosphorylation under physiological conditions (37) and to initiate apoptosis when the ER Ca^{2+} load increases exaggeratedly (175). MAMs are also enriched in ER chaperones, in oxidoreductases, and in lipid metabolism enzymes and, consistent with this molecular composition, have been implicated in the regulation of protein folding and of lipid exchange [reviewed in further detail in (24, 77, 158)].

ROS Sources and Redox Signaling

ROS sources

The term ROS generally refers to a collection of chemical species derived from molecular oxygen including superoxide radicals ($O^{2-}\bullet$), hydrogen peroxide H_2O_2, hydroxyl radicals ($OH\bullet$), hydroperoxyl radicals ($OH_2\bullet$), and hypochloric acid (HOCl). Reactive nitrogen species (RNS), derived from the reaction of superoxide with nitric oxide ($NO\bullet$) are often considered together with ROS because of the similarity in their reactive chemistry (14, 201). While historically ROS were viewed as toxic substances that damage biomolecules, it is now well recognized that cells sense ROS by a variety of mechanisms, and that ROS serve as important signaling molecules both in physiological conditions and under stress. Cellular ROS can arise as a consequence of exposure to environmental factors such as chemical oxidants or high-energy radiation, but may also be purposely produced by endogenous enzymes such as NADPH oxidases (NOX) and dual oxidases (DUOX) (9). Alternatively, ROS may be generated either as a byproduct or through unwanted side reactions. Prominent sources include the arachidonic acid metabolizing enzymes such as cyclooxygenases, lipoxygenases, and cytochrome P450; catabolic enzymes such as xanthine oxidase; cytochromes of the electron transport chain (ETC); and ER oxidoreductases that support oxidative protein folding such as the ER oxidase (Ero) family proteins and quiescin-sulfhydryl oxidase (QSOX) (96), (summarized in Fig. 2).

While ROS can be produced in a compartmentalized manner, some species such as H_2O_2 can cross cellular membranes, and facilitated transport by certain types of aquaporins extends its diffusion range (13). In addition, in immune cells such as neutrophils, NOX proteins shuttled to the PM can generate large amounts of extracellular superoxide (89). Endogenous ROS sources can therefore act in a paracrine manner and potentially cause oxidative damage to other cells. Indeed phagocytes expressing high levels of NOX2 can produce up to millimolar levels of superoxide when they ingest foreign particles as part of the antimicrobial defense mechanism (202) rendering NOX proteins likely the most potent sources of endogenous ROS. In all cells, mitochondria complex I and III of the ETC produce ROS as an unwanted side-reaction during oxidative phosphorylation. Under resting conditions, the mitochondrial superoxide concentration has been estimated to be 5–10-fold higher than in the cytosol and nuclear compartments (26), an output that can increase under certain conditions of stress. Mitochondrial ROS has been postulated to significantly contribute to the accumulated protein and lipid damage that naturally occurs during aging (162) and in various pathologies mitochondria are viewed as primary sources of ROS (26, 31, 56). In recent years, enzymes involved in oxidative protein folding in the ER have been increasingly recognized as another prominent site of ROS production. Protein-disulfide isomerases (PDI), the enzymes responsible for disulfide bond formation, require electrons, which ultimately come from molecular oxygen *via* Ero1 family ER oxidoreductases or QSOX, that directly produce H_2O_2 as a byproduct (30, 96, 193, 194). When mutations increase Ero1 activity or when the activities of oxidoreductases such as Prx4, GPx7, and GPx8 that consume ER H_2O_2 are compromised, the ER can become hyperoxidized (30, 125, 177). Like mitochondria, the ER consumes oxygen (193, 194), although precise measurements of how much oxygen the ER consumes as compared to mitochondria are still lacking. Most cells have low but significant non-mitochondrial oxygen consumption (23). This has been estimated to be between 10%–20%, usually either by measuring oxygen consumption rates in the presence of rotenone or other ETC inhibitors, or by generating cell lines lacking mitochondrial DNA, the so-called "rho 0" cells (122, 129). However, it remains unclear how much of the remaining oxygen consumption is utilized in the ER *versus* cytosol or within other organelles, and more importantly whether inhibiting mitochondrial function affects ER oxygen consumption. Interestingly, a recent study showed that increasing secretory protein load augments cellular oxygen consumption without increasing oxidative phosphorylation, suggesting the ER adapts its oxygen consumption to its oxidative protein folding requirements (195). The ER may in fact have a higher H_2O_2 content than mitochondria under

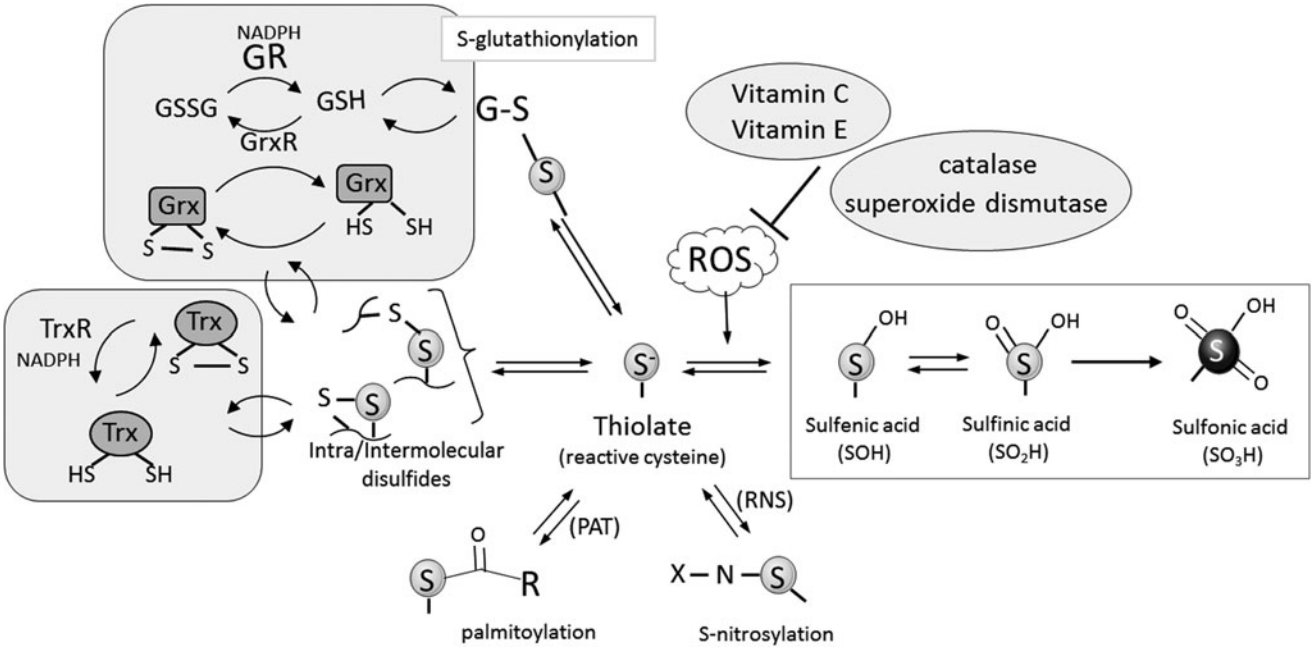

FIG. 3. ROS signaling and antioxidant systems. Key events in ROS signal transduction occur through modification of reactive cysteine residues that predominantly exist as thiolate ions due to their protein microenvironment. Thiolate side chains may be directly oxidized by ROS to sulfenic, sulfinic, or irreversibly to sulfonic acid, or by reactive nitrogen species (RNS) resulting in S-nitrosylation. Fatty acids may be reversibly bonded to thiolate side chains by protein acyltransferases (PAT), while reaction with intra- or intermolecular thiolates will result in disulfide bond formation. Thiolate side chains may be protected from oxidation by reaction with endogenous antioxidant glutathione (GSH) termed S-glutathionylation; while glutaredoxin and thioredoxin (Trx) systems utilize GSH and Trx respectively to reduce disulfides. Other cellular antioxidant systems include enzymes that catabolize ROS such as catalase and superoxide dismutase and chemical antioxidants such as vitamin C and E.

resting conditions (53). Moreover, inhibition of oxidative protein folding or modifications of the ER redox environment and other insults leading to ER stress are associated with higher levels of ER-derived ROS (68, 95, 171). Thus, in addition to the mitochondria the ER should also be considered as an important source of ROS both in physiological and pathophysiological conditions, and future studies should aim to more carefully examine extra-mitochondrial oxygen utilization and its products.

ROS signaling, antioxidant mechanisms, and oxidative stress

One of the principle mechanisms underlying ROS signaling is based on direct modification of reactive cysteines (Fig. 3). The cysteine sulfhydryl side chain (-SH) has a pKa of ~8 but the microenvironment within a protein polypeptide, defined by the three-dimensional arrangement and nature of neighboring side chains, can reduce this value to ~4–5 effectively rendering it a more reactive nucleophilic thiolate ion (-S-) at physiological pH. It follows that protein conformational changes and changes in cytosolic or intraorganellar pH might inhibit or promote the reactivity of particular cysteines. H_2O_2 can directly oxidize thiolate side chains sequentially to sulfenic (-SOH), sulfinic ($-SO_2H$) and, at higher oxidant concentrations, to sulfonic acid ($-SO_3H$), which is irreversible and generally considered to represent oxidative damage. Other cysteine modifications include intra or intermolecular disulfide formation and palmitoylation. Disulfide formation may either be enzymatically catalyzed as is the case during oxidative protein folding, or spontaneously occur when thiolate side chains are in close proximity. Oxidizing conditions and alkaline pH can promote disulfide formation by favoring cysteine side chains to exist in the thiolate state. However, further thiolate oxidation may hinder recognition and catalysis by PDI. Similarly, although palmitoylation is stricktly dependent on palmitoyl transferases and acyl esterases, enzyme recognition may again be either promoted by sulfhydryl deprotonation or hindered by thiolate oxidation. Akin to phosphorylation, modification of reactive cysteines can have profound effects on protein activity either by inducing conformational changes or by modifying the binding of functional partners (82, 119).

To protect thiolate side chains and prevent permanent oxidative damage to proteins, S-glutathionylation (–S-SG), the addition of the tripeptide glutathione (GSH) to a reactive cysteine (40), is an important antioxidant defense mechanism (Fig. 3). In addition to the GSH-glutaredoxin system, other antioxidant mechanisms include the expression of superoxide dismutase (SOD) and catalase that catabolize superoxide directly, molecular antioxidants such as vitamin C and E, and the thioredoxin (Trx) system that can swap disulfide bonds with oxidized proteins. The Trx system acts in concert with GSH to maintain cellular redox homeostasis although the crosstalk between these two systems is not entirely understood (6, 82, 113). Hence, the duration and dynamics of cystein modifications can be difficult to predict as they depend not only on the residue microenvironment within the protein, the

type and length of exposure to the oxidant, and thiolate oxidation state, but also on the overall status of the antioxidant systems (*i.e.*, GSH/GSSR and Trx^{red}/Trx^{ox} ratios and levels of endogenous ROS scavenger enzymes and molecules). When oxidant levels exceed the capacity of these multiple antioxidant systems to absorb excess ROS, or when antioxidant systems themselves become compromised, the cell enters a state of oxidative stress. In addition to being an antioxidant, Trx is a major oxidative stress sensor as redox modulation of Trx binding to its partners TXNIP and ASK1 can induce inflammasome activation and apoptosis, respectively (113). A second major sensor and perhaps one of the most important regulators of oxidative stress is nuclear factor (erythroid-derived 2)-like 2 (Nrf2). Binding of this transcription factor to its repressor Kelch-like ECH-associated protein 1 (Keap1) in the cytosol normally targets it for proteasomal degradation. Both Nrf2 and Keap1 have several reactive cysteines that regulate their binding in a redox-sensitive manner, and dissociation of Nrf2 from Keap1 allows its translocation to the nucleus where it initiates downstream transcriptional cascades (76, 119). Nrf2 targets include enzymes boosting GSH synthesis and conjugation such as glutamate cysteine ligase, cysteine-glutamate transporters, GSH S-transferases, and GSH reductase; Trx reductase, TXNIP, and Trx itself; ROS-consuming enzymes such as SOD3, peroxiredoxin, and several GSH peroxidases; autophagy-promoting protein p62; among many others that together limit further protein and lipid oxidative damage, increase the degradation of damaged biomolecules, and if necessary, trigger inflammation or apoptosis (119). In addition to direct thiol modification, Nrf2 activation is regulated by a variety of other mechanisms including direct phosphorylation by the ER stress sensor protein kinase R-like ER kinase (38, 39), linking ER redox homeostasis to oxidative stress responses.

ROS regulation of SOCE can be defined in terms of two principle effects: (i) *via* direct effects on the core SOCE machinery, including STIM proteins and their partner channels, or (ii) indirectly by influencing the status of ER Ca^{2+} stores. Taking regulatory mechanisms outlined here into account one can envision that these effects may occur *via* direct oxidation and cysteine modification of the proteins in question or by triggering oxidative stress and stress responses that then influence the SOCE machinery by pre or post-translational mechanisms. A third mechanism that will be briefly discussed is the fact that production of charged ROS such as superoxide can directly influence the ionic balance across cellular and intracellular membranes or indirectly induce changes in ion concentrations that then affect electrochemical forces driving Ca^{2+} fluxes (51). In the following sections rather than providing a comprehensive account of the vast literature examining the relationship between ROS and SOCE, we will focus on summarizing more recent advances in our understanding of how each of the above ROS-dependent mechanisms affect SOCE.

Redox Control of the Core SOCE Machinery

The literature addressing the role of ROS in the control of SOCE is replete with conflicting data. The number of studies establishing that exposure to oxidants increases SOCE by favoring ER Ca^{2+} depletion (50, 81, 130, 145, 153, 192) and more recently (70) are nearly matched by those supporting a role for ROS in diminishing SOCE (59, 173, 191, 215), while others still report time-, dose-, and reactive species-dependent effects (52, 159, 160). As our understanding of SOCE has grown since the discovery of STIM and Orai proteins, it is likely that one of the major reasons underlying these discrepancies are cell-type differences, since the SOCE machinery changes depending on cell type. For example, neurons and dendritic cells use STIM2 instead or in addition to STIM1, muscles employ STIM1L isoforms, and endothelial and myoblasts cells engage TRPCs in addition to Orai (3, 41, 184). Additionally, over the past few years it has become apparent that nearly all of the molecular machinery governing SOCE and ER Ca^{2+} content contain reactive thiols that are directly modified under different oxidative conditions. The fact that different thiol modifications may have different functional outcomes (*e.g.*, disulfide formation may be different than S-glutathionylation, which in turn may be different than irreversible sulfonylation), adds a critical factor that can account for the variability observed. Thus, to formulate a more complete understanding of how ROS and oxidative stress govern SOCE it is necessary to obtain a deeper understanding of exactly which amino acids in proteins comprising the molecular machinery governing SOCE can be modified by ROS directly, what type of modifications are made, and how each type of modification affects the function of each molecule.

Redox control of STIM proteins

A prominent advance in understanding redox control of SOCE was the first demonstration that STIM1 is redox sensitive (75). In this study, STIM1 was shown to be S-glutathionylated on a conserved cysteine residue C56 located just prior to the luminal Ca^{2+}-binding EF-hand domain during oxidative stress induced by bacterial lipopolysaccharide (LPS) or butathionine sulfoximine-induced GSH depletion in B leukocytes (75). S-glutathionylation lowered the affinity of STIM1 for Ca^{2+} and facilitated oligomerization, leading to store-independent activation of STIM1. Using a combination of protein mobility assays, immunoblotting and mass spectrometry, the authors determined that neither C56 nor another conserved cysteine C49 were directly oxidized by H_2O_2 and that only C56 is S-glutathionylated under oxidative conditions. Further, C56A mutation resulted in constitutive activation of SOCE, confirming the role of this residue in regulating STIM1 activity (Fig. 4A).

In addition to modulating STIM1 oligomerization, C56 together with C49 were found to modulate STIM1 binding to the oxidoreductase ERp57 in mouse embryonic fibroblasts (156). ERp57 is a protein of the Trx family that together with PDI is largely responsible for oxidative protein folding and quality control in the secretory pathway (34). Mammalian ERp57 also modulated SERCA function when both were heterologously expressed in a *Xenopus* oocyte system, and may therefore be linked to ER Ca^{2+} homeostasis (109) (see also the Redox Control of ER Ca^{2+} Stores section below). ERp57 was found to bind to STIM1 by surface plasmon resonance and fluorescence-energy transfer (FRET) and its deletion potentiated STIM1 puncta formation and SOCE while ERp57 overexpression had the opposite effect (156). Based on differences in electrophoretic mobility the authors suggested that a disulfide bond between C56 and C49 occurs under normal conditions, but that ERp57 is not required for its

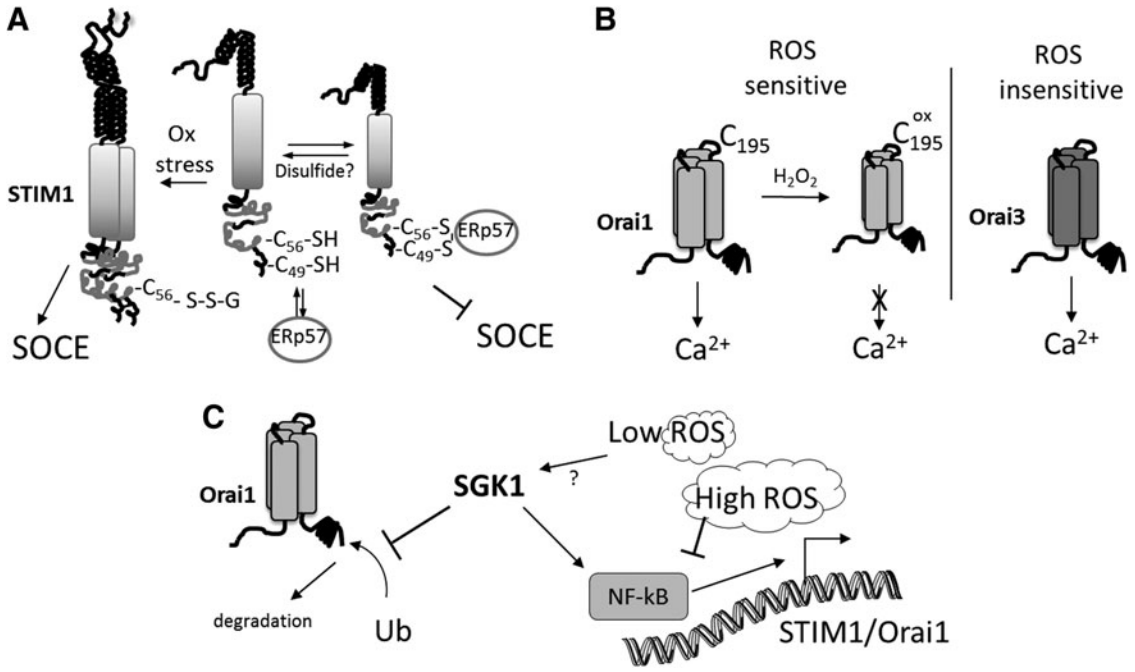

FIG. 4. Redox regulation of SOCE core machinery. (A) STIM1 proteins are directly redox sensitive *via* two luminal cysteines C56 and C49. S-glutathionlyation at C56 facilitates SOCE activation during oxidative stress while disulfide formation may inhibit SOCE by promoting ERp57 binding. **(B)** Oxidation of an extracellular cysteine C195 abrogates Ca^{2+} entry through Orai1 but not redox insensitive Orai3 channels. **(C)** Serum/glucocorticoid-activated kinase 1 (SGK1) activity increases Orai1 abundance both by inhibiting its ubiquitin (Ub)-mediated degradation and by activating nuclear-factor kappa B (NF-κB), a transcription factor that promotes expression of both Orai1 and STIM1. Low levels of ROS activates NF-κB while higher levels are inhibitory, suggesting that transcriptional and post-translational control of SOCE core machinery abundance may be biphasic.

formation. FRET experiments using a C56A/C49A mutant suggested that disulfide bond formation may enhance ERp57 binding. In direct contrast to the study by Hawkins *et al.* (75) these authors observed that C49A/C56A mutation inhibited STIM1 puncta formation and SOCE. Thus, while it is clear that C56 is an important residue in regulating STIM1 function, future research must determine whether the discrepancies arise because of differences in cellular models or whether the nature of C56 modification plays a role in different conditions to clarify exactly how STIM1 is regulated by ROS (Fig. 4A). It is worth mentioning that both STIM2 and STIM1L isoforms contain conserved and putative reactive cysteines that have yet to be explored. For a more detailed discussion on the potential redox regulation of other STIM isoforms the readers are referred to the following recent reviews (14, 15).

Redox control of SOC channels

In addition to STIM1, Orai1 was also recently demonstrated to act as a direct redox sensor mainly by virtue of a reactive cysteine at position C195 located in an extracellular loop, although C126 and C142 also contributed but to a much lesser extent (16). Using patch clamp and Ca^{2+} imaging, Bogeski *et al.* (16) showed that exposure to H_2O_2 inhibited Ca^{2+} influx through Orai1, but that mutation of the three cysteines to non-oxidizable serines completely abrogated redox sensitivity and reaction with the free thiol detector 5,5′-dithiobis-(2-nitrobenzoic acid) 2 biotin. In contrast Orai3, which lacks C195 in its homologous position, was insensitive to redox regulation, and its co-expression with Orai1 reduced SOCE sensitivity to ROS inhibition. Importantly, T lymphocytes were found to upregulate Orai3 expression during differentiation into effector T cells, suggesting that regulation of the Orai1:Orai3 ratio may represent an important mechanism by which immune cell survive in highly oxidative environments during inflammation. Interestingly, although H_2O_2 inhibition of Orai1 was fast acting, addition of H_2O_2 to preactivated cells failed to inhibit SOCE currents, indicating that predocked STIM/Orai complexes may be resistant to oxidative inhibition. The exact mechanism by which H_2O_2 inhibits Orai1 function (*i.e.*, by reducing channel permeability, oligomerization, or interaction with STIM proteins) remains to be defined. However, it should be noted that future research in this area will need to consider other parameters indirectly controlling Orai activity, exemplified by the recent report of Grupe *et al.* who observed an increase rather than a decrease in Orai-mediated Ca^{2+} influx in response to H_2O_2 that was explained by oxidation-dependent activation of IP_3R activity rather than modification of Orai itself [(70), see also discussion on IP_3R below, Fig. 4B].

In addition to Orai proteins, channels of the TRPC1, 3, 4, and 5 can exhibit SOC channel activity, although this appears to be highly dependent on cell type (143). STIM1 has also been shown to partner with L-type Ca^{2+} channels (132). Various TRPC channels including TRPC3, 4, and 5 are redox sensitive (154, 205) as are L-type channels (83). Thus, the redox sensitivity of SOCE in a particular cell type might depend on the constellation of STIM1-gated Ca^{2+}-permeable channels expressed at the PM. We refer the reader to two additional reviews

in the current ARS Forum for further information on redox regulation of TRPs and of voltage-activated Ca^{2+} channels.

Redox control of cytosolic Ca^{2+} levels

Another factor regulating the core SOCE machinery is cytosolic Ca^{2+} levels. High cytosolic Ca^{2+} promotes Ca^{2+}-dependent inactivation of Orai1, dissociation of Orai1 from STIM1 molecules, and STIM1 inactivation (48, 105, 178). Redox modifications can also regulate Ca^{2+} extrusion from cells as reactive thiols have been detected and investigated in both NCX (79, 87, 161) and PMCA (92, 211, 212). While more recent studies support the idea of oxidation increasing NCX activity (99) the exact mechanisms remain unclear as cysteine mutations also promote NCX activation (169). In contrast, oxidation reduces PMCA activity (92, 211, 212) by a mechanism that likely involves disulfide bond formation (212), although the exact residues involved remain unidentified and have even been suggested to be tyrosine or methionine rather than cysteines (117). Interestingly, calmodulin binding may protect PMCA from oxidation adding another layer of redox regulation on Ca^{2+} extrusion from cells (79, 148, 212).

Redox control of SOCE core machinery abundance

Numerous transcriptional regulators are redox sensors (200) and oxidative stress additionally triggers transcriptional programs that could potentially affect SOCE (119). While numerous binding partners of STIM1 have now been identified, less is known about the transcriptional and post-translational mechanisms that regulate STIM and Orai protein abundance. Recently, *Stim1* and *Orai1* transcription was shown to be enhanced by direct promoter binding of nuclear factor kappa B (NF-κB) (55), a transcription factor central to inflammation and immunity that has a complex interrelationship with cellular ROS production and cellular responses to ROS (133). Current views postulate that low levels of ROS activate NF-κB activity while higher levels are inhibitory (91, 200), and that Nrf2 activation opposes NF-κB action (108). Given that the human *Orai1* promoter additionally contains a putative Nrf2-binding site, it is thus tempting to speculate that downregulation of STIM/Orai proteins *via* oxidative inhibition of NF-κB could serve as protective mechanism during oxidative stress. Indeed reduced Orai expression was recently shown to be protective against cell death induced by GSH depletion (78). However, serum/glucocorticoid-activated kinase 1, a kinase that is upregulated during oxidative stress (21, 106), enhanced Orai1 abundance by inhibiting its ubiquitin-mediated degradation, and by activating NF-κB (21, 54, 102). Thus, the oxidant to antioxidant ratios and the degree of oxidative stress may be important factors in fine-tuning the abundance of the SOCE core machinery (Fig. 4C). Interestingly, two studies have reported that siRNA knockdown of Orai3 can increase *Orai1* transcript levels (71, 127), indicating that Orai isoform expression may be coordinated. While the *Orai3* promoter does not contain canonical NF-κB binding sites, it does contain putative sites for CCAAT-enhancer-binding protein homologous protein (CHOP) and X-box-binding protein 1, transcription factors triggered downstream of ER stress. Whether ER stress contributes to the upregulation of Orai3 expression that protects T cells from highly oxidizing conditions during inflammation (16) awaits further study. Additionally, we observed that while all Orai proteins were able to localize to phagosomes, organelles that produce high levels of ROS, where they contributed to STIM1-mediated periphagosomal Ca^{2+} microdomains, Orai3 was preferentially enriched while Orai1 was depleted on phagosomes [(139) and unpublished observations]. Whether local abundance of Orai1 and Orai3 proteins are ROS mediated is an intriguing possibility that has yet to be explored. In summary, high oxidant levels trigger competing factors in the regulation of the activity of STIM proteins and their partner channels and their abundance and localization, the balance of which may determine whether SOCE is upregulated, increasing danger signals and inflammation or whether it is downregulated, protecting cells from toxicity associated with Ca^{2+} overload.

Redox Control of ER Ca^{2+} Stores

Redox control of ER Ca^{2+} retention

ER Ca^{2+} levels are defined by the balance of ER Ca^{2+} loss through leak or release pathways with respect to the accumulation of ER Ca^{2+} promoted by SERCA pumps. There are 22–28 cysteines on SERCA depending on the isoform, and many studies agree that SERCA pumping is inhibited by ROS (7, 69, 94, 204). More recently, Kuster *et al.* (99) directly demonstrated that exposure to ROS is correlated with reduction of free thiols in SERCA using biotinylated iodoacetamide labeling. The type of cysteine modification is important, however, as S-glutathionylation of C674 activated SERCA, while sulfonylation of various cysteines including C674 were correlated with reduced SERCA activity (1), and led to SERCA targeting for degradation (208). RNS may also increase SERCA activity, thereby inhibiting SOCE (19, 35). Interestingly, mutation of two luminal cysteines C875 and C887 also increased rat SERCA2b activity (109). In this study, the authors found that human ERp57 interacts with these luminal cysteines when both proteins were expressed in *Xenopus* oocytes, inhibiting SERCA2b under oxidizing conditions. ERp57 oxidase activity was required for this inhibition, implying that ERp57 inhibits SERCA2b by promoting an intramolecular disulfide bond formation between C875 and C887. The interaction with ERp57 was reduced at low ER Ca^{2+} suggesting that ERp57 dissociation may contribute to the mechanism by which SERCA senses and is activated by low ER Ca^{2+}. Calnexin and calreticulin associate with ERp57 (140) and interaction of SERCA2b with phosphorylated calnexin also inhibits SERCA activity (167), further suggesting that recruitment of ERp57 contributes at least in part to this inhibition. Thus, ERp57 appears to exert opposing effects on SOCE depending on its binding partner, enhancing ER Ca^{2+} depletion *via* SERCA2b to promote SOCE, while inhibiting STIM1 clustering and activation to decrease SOCE. Clearly more work will be required to decipher exactly how ERp57 effects are coordinated under differing oxidative conditions.

Redox control of ER Ca^{2+} release

Many of the early studies investigating the role of ROS on SOCE reported that ROS sensitized SOCE activation by depleting ER Ca^{2+} stores. While inhibition of SERCA activity is one way to deplete Ca^{2+} stores, activation of Ca^{2+} release or leak *via* RyR and IP_3R can also contribute. RyR are large ($\sim$2.3 MDa) molecules with numerous ($>$100) cysteines that have a long history of reports documenting their redox

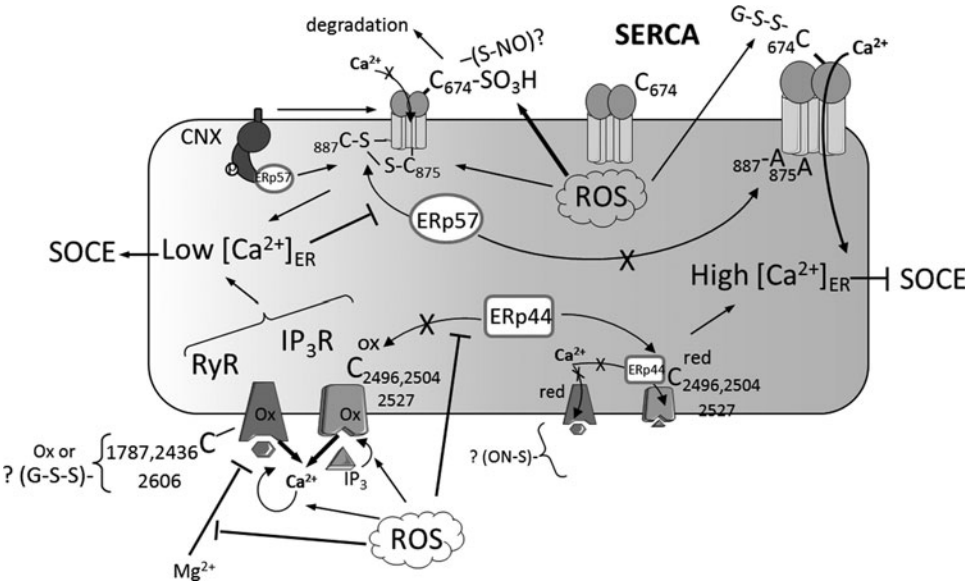

FIG. 5. Redox regulation of ER Ca^{2+} content. Oxidation of SERCA pumps, including sulfonation, disulfide formation, and possibly nitrosylation inhibit ER Ca^{2+} refilling, facilitating SOCE activation (*top left*, light gray indicates depleted ER Ca^{2+} stores). Inhibition may be caused by direct reduction in SERCA activity, increased degradation, and by increased recruitment of ERp57, which may be further enhanced by phosphorylated calnexin (CNX) binding. S-glutathionylation at C674 (SERCA1) and C887,875A mutations (SERCA2b) that inhibit ERp57 binding both increase SERCA activity, inhibiting SOCE (*top right*, dark gray indicates overfilled ER Ca^{2+} stores). S-glutathionylation and oxidation(ox) at multiple cysteines including C1787,2436 and 2606 (RyR2) activate RyR by both reducing Mg^{2+} inhibition and promoting calcium-induced Ca^{2+} release, facilitating SOCE (*bottom left*). Similarly, oxidation of multiple cysteins including C2496,2504 and 2527 (IP_3R1) promote IP_3R activity by increasing IP_3 affinity and by inhibiting ERp44 binding. S-nitrosylation and ERp44 binding to reduced (red) luminal cysteines reduce IP_3R activity and inhibit SOCE (*bottom right*).

sensitivity [see (79, 104) for recent reviews]. Recent mass spectrometric analysis confirmed that as many as 60 cysteine residues display reactivity to thiol probe monobromobimane, with C1781, C2436, and C2606 in RyR1 playing prominent roles in regulating RyR activity (149). In general, oxidation promotes RyR activation both by increasing calcium-induced Ca^{2+} release and decreasing Mg^{2+} inhibition (72, 189) and therefore promotes depletion of ER Ca^{2+}, activating SOCE. Important reversible modifications include *S*-nitrosylation, *S*-glutathionylation, and disulfide oxidation, with more recent analyses of RyR2 suggesting that only S-glutathionylation is activating, while S-nitrosylation, which is reduced by oxidation, may in fact be inhibitory (28, 67).

Similar to RyR, numerous studies in the 90's have suggested that oxidation of IP_3Rs promotes their activity. A common theme emerged showing that direct oxidation of IP_3R increases receptor affinity for IP_3 (20, 112, 130, 172, 196). In one study, thiol oxidation of IP_3R1 but not IP_3R3 induced a conformational change in the cytosolic N-terminus that was suggested to be responsible for the increased affinity of the oxidized receptor to IP_3 (29). Further, oxidoreductase ERp44 binding of IP_3R1 but not IP_3R2 or 3 inhibited channel activity in planar lipid bilayers. The interaction was diminished by low pH, high ER calcium, and required free thiols in luminal loop cysteines C2496, C2504, and C2527 but not ERp44 catalytic activity (80), suggesting that oxidative conditions additionally activate IP_3R at least in part through loss of ERp44 binding. A later study suggested that conformational changes due to disulfide formation in the same luminal loop may additionally affect IP_3R1 activity (93). Together, these studies confirm that IP_3R activity is not only regulated by ROS on the cytosolic side but that it is also intimately tied to ER luminal redox homeostasis (Fig. 5). This indirect mechanism of SOCE activation by ROS is of high clinical relevance because NOX2-mediated endogenous ROS production was recently shown to mediate the increased permeability of the pulmonary endothelium during LPS-induced inflammation by activating IP_3R2 and promoting STIM1-dependent SOCE (63).

Redox regulation of SOCE at the ER-mitochondria interface

IP_3Rs are enriched in subdomains of the ER that make intimate contact sites with mitochondria (MAMs) where they directly associate with mitochondrial outer membrane protein VDAC and transfer Ca^{2+} from the ER to mitochondria with minimal loss to the cytosol (165, 188). Since the proximity of mitochondria at MAMs allows them to rapidly absorb the Ca^{2+} ions released from IP_3R, they can regulate IP_3R activity by reducing Ca^{2+}-dependent inactivation (17, 73, 101, 164). Therefore, MAMs potentially influence luminal ER Ca^{2+} (Fig. 6). Interestingly, overexpression of wild-type or presenilin-2 (but not presenilin-1) mutants associated with familial Alzheimer's disease, a protein also enriched in MAMs (4), lead to an increase in ER-mitochondria interaction and Ca^{2+} transfer at MAMs (213), which was suggested to lead to ER Ca^{2+} depletion (27, 214) and more recently directly to increased mitochondrial ROS production (135). Yet, another link between ROS and IP_3R activity was uncovered whereby Ero1α, an H_2O_2-producing ER oxidoreductase recently shown to localize almost exclusively to MAMs under normoxic but not reducing conditions (66, 182), regulated IP_3R activity by

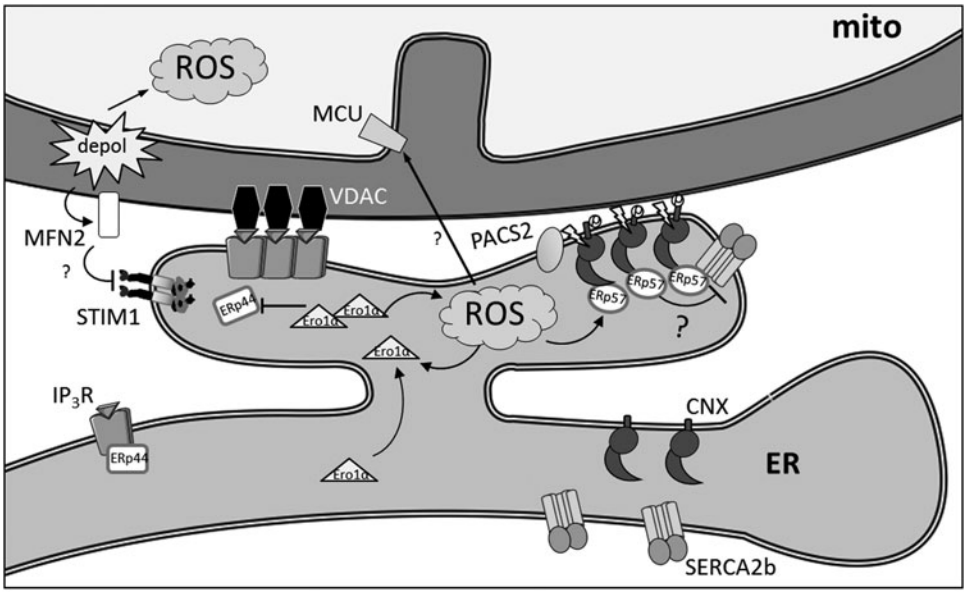

FIG. 6. Potential redox regulation of SOCE at ER-mitochondrial contact sites. MAMs enriched in IP_3Rs coupled to mitochondrial ion transporter VDAC facilitate Ca^{2+} transfer from ER to mitochondria and its subsequent reuptake by SERCA. MAMs are therefore important platforms for the regulation of ER Ca^{2+} content and SOCE activation. Ero1α is enriched in MAMs in a redox-dependent manner, and its ROS-generating activity inhibits ERp44 binding to IP_3R while promoting mitochondrial Ca^{2+} uptake *via* the MCU. MAM-resident marker PACS2 binding promotes MAM accumulation of palmitoylated, phosphorylated CNX, which may in turn inhibit SERCA2b by promoting ERp57 binding. Mitochondrial depolarization, an event that promotes mitochondrial ROS production, inhibits STIM1 activation through an incompletely understood mechanism that requires mitochondrial but not ER-localized mitofusin-2 (MNF2).

inhibiting its binding to ERp44. Surprisingly, in a study by a different group, silencing, and overexpressing wild-type or a catalytically dead Ero1α (C394A) mutant, demonstrated that Ero1α expression had only minor effects on ER Ca^{2+} levels and did not affect SERCA2b activity. Instead, Ero1α had a major impact on mitochondrial Ca^{2+} uptake, and the data suggested this was due to an effect on the activity of the MCU (2). Human MCU has five conserved cysteines two of which (C26 and C33) are in the matrix N-terminal tail. Whether MCU is itself redox sensitive remains to be verified. Ero1α expression is induced by the ER stress effector CHOP, promoting ER hyperoxidation under conditions of ER stress (123). Indeed, CHOP and Ero1α expression and activity were both required for triggering IP_3R-mediated ER Ca^{2+} release (107), a critical step in ER-stress induced apoptosis (176), indicating that under stress conditions Ero1α can in fact regulate ER Ca^{2+} content.

Interestingly, palmitoylation on C503/C504 of calnexin modulates its localization within the ER (100) and may enhance calnexin retention in MAMs (118), suggesting calnexin localization may be redox sensitive. Although SERCA does not appear to particularly accumulate in MAMs in contrast to IP_3Rs, Ca^{2+}-dependent dephosphorylation of rat calnexin was proposed to decrease its clamp on SERCA activity during ER stress in a heterologous *Xenopus* oocyte system (18, 167). Since in mammalian cells MAM marker phosphofurin acidic cluster sorting protein (PACS2) promoted the retention of dephosphorylated calnexin (136), and ER stress promotes calnexin localization to heavy ER fractions consistent with MAMs (46) an additional redox dependent mechanism by which SERCA activity and therefore ER luminal Ca^{2+} may be regulated is *via* sequestration of inhibitory binding partners of SERCA such as calnexin within MAM ER subdomains (182). Admittedly, that these mechanisms persist in different mammalian cell types awaits verification.

Finally, another link between mitochondria and SOCE was recently revealed by Singaravelu *et al.* who showed that mitochondrial depolarization inhibits STIM1 trafficking to ER-PM junctions (183). Here, the authors showed that the MAM tether mitofusin-2 (MFN2) was strictly required for mitochondrial depolarization to inhibit STIM1 trafficking, and that SOCE inhibition was independent of mitochondrial Ca^{2+} buffering. However, the mechanism by which MFN2 regulates STIM1 trafficking is still unknown. In light of the fact that oxidative damage can lead to mitochondrial depolarization (137, 138), elegantly illustrated recently in two reports utilizing a genetically encoded photosensitizer targeted to mitochondrial to induce specific mitochondrially localized ROS (199, 206), MFN2 may thus represent an important transducer of ROS signals to SOCE.

Redox Reactions and Ionic Balance

The dependence of redox reactions on pH is well known and stems from intrinsic properties of redox chemistry: loosing protons usually increases nucleophilicity, and the redox potential of electron donors and acceptors is usually defined at a given pH (14). As mentioned earlier, thiolate modifications are likely affected by cytosolic pH, which may dramatically change under certain conditions such as neuronal or myocardial ischemia and cancer (32, 111, 190). Therefore, redox signaling could change solely based on indirect changes in intracellular ionic composition, although in the case of SOCE deciphering which changes are redox dependent or not

maybe complicated by the fact that non-redox related electrostatic interactions are also influenced by cytosolic ionic factors such as pH (121). Conversely, redox reactions can alter ionic balance, as clearly illustrated during superoxide production by NOX that are electrogenic transmembrane proteins that transport electrons across their resident membranes. NOX generate cytosolic protons from NADPH, and additionally require concomitant proton transport across the resident membrane to prevent excess depolarization, which can reach up to −180 mV in the absence of charge compensation and lead to self-inhibition of the enzyme (45). Interestingly, in our recent studies on the dependence of the phagocyte NOX2 activity on proton transport *via* the Hv1 proton channel we found that a secondary consequence to depolarization occurring with oxidase activity in the absence of Hv1 was an inhibition of Ca^{2+} influx that could be explained by the decrease in the electrochemical driving force for Ca^{2+} to enter the cell (51). Although we did not examine SOCE directly in this study, it did bring up the intriguing consideration that Ca^{2+} fluxes occurring in the context of the production of charged ROS species can be influenced by disturbances on the intracellular ionic balance. Indeed, sodium influx *via* the promiscuous cation channel TRPM2 was recently proposed to provide a negative feedback loop for controlling excess ROS production by promoting membrane depolarization (49). Hence, yet another parameter to consider is that positive and negative feedback loops linking Ca^{2+} or other ionic fluxes to ROS production may additionally propel or inhibit redox signaling.

Concluding Remarks

Alterations in cellular calcium and redox homeostasis directly affect the function of the heart, brain, and immune system, leading to debilitating diseases with high morbidity such as cardiac arrhythmia and hypertrophy, Parkinson's and Alzheimer's disease, stroke, acute and chronic inflammation, and immune deficiencies (11). Understanding the complex relationship between the calcium-handling machinery and the oxidative systems that produce the endogenous ROS required for proper cellular function is therefore of major clinical relevance. The ubiquitous store-operated entry pathway, which relies on the coordinated function, redistribution, and interactions of Ca^{2+}-handling proteins on the ER and on the PM, is particularly exposed to local redox alterations occurring at membrane contact sites between the ER and mitochondria, where store depletion is initiated, and between cortical ER subdomains and the PM, where SOCE channels activate and inactivate. To understand how ROS regulate SOCE we must first establish the exact nature of the redox modifications modulating the activity of proteins controlling the initiation, maintenance, and termination of the SOCE process. In particular, the challenge for future researchers will be to develop novel technologies that will allow us to more precisely map the residues in proteins of the SOCE machinery that are subject to redox modifications, to determine which modifications occur under which conditions, and to define the consequence of each type of modification on the protein's function. Then, we should fully decipher the pre- and post-translational control of the SOCE machinery to clarify how signaling pathways triggered by oxidative stress indirectly influence SOCE. Finally, we should obtain a better knowledge of the chemical events occurring at membrane contact sites to model how local interactions between the ROS and SOCE signaling systems impact on the coordinated fluxes of calcium occurring across multiple organelles under physiological and stress conditions.

Acknowledgments

Our work is funded by the Swiss National Science Foundation grant number *N°* 310030B_133126 (to N.D.). Figures were produced using modified graphics from Servier Medical Art (www.servier.com).

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Date of first submission to ARS Central, September 6, 2013; date of acceptance, September 22, 2013.

Abbreviations Used

CHOP = CCAAT-enhancer-binding protein homologous protein
CNX = calnexin
DUOX = dual oxidase
ER = endoplasmic reticulum
ERO = endoplasmic reticulum oxidase
ERp44 = endoplasmic reticulum protein of 44 kilodaltons
ERp57 = endoplasmic reticulum protein of 57 kilodaltons
ETC = electron transport chain
FRET = fluorescence-energy transfer
GPX = glutathione peroxidase
IP_3 = inositol 1,4,5 phosphate
IP_3R = IP_3 receptor
Keap1 = kelch-like ECH-associated protein 1
LETM1 = leucine zipper EF hand-containing transmembrane protein 1
LPS = lipopolysaccharide
GSH = glutathione
MAM = mitochondria-associated membrane
MCU = mitochondrial Ca^{2+} uniporter
NCLX = sodium-calcium exchanger, mitochondrial
NCX = sodium-calcium exchanger
NF-κB = nuclear-factor kappa B
NOX = NADPH oxidase
Nrf2 = nuclear factor (erythroid-derived 2)-like 2
PACS2 = phosphofurin acidic cluster sorting protein
PDI = protein disulfide isomeriase
PM = plasma membrane
PMCA = plasma membrane calcium ATPase
PRX = peroxiredoxin
QSOX = quiescin-sulfhydryl oxidase
ROS = reactive oxygen species
RyR = ryanodine receptor
SERCA = sarcoendoplasmic reticulum calcium ATPase
SGK1 = serum/glucocorticoid-activated kinase 1
SOCE = store-operated calcium entry
STIM = stromal interaction molecule
Trx = thioredoxin
Tg = thapsigargin
TRPC = transient receptor potential channel, canonical
Ub = ubiquitin
VDAC = voltage-dependent anion channel
Xbp-1 = X-box-binding protein-1