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Review

The ER and ageing II: Calcium homeostasis

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ABSTRACT

Increase in intracellular Ca^{2+} concentration occurs by Ca^{2+} influx through the plasma membrane and by Ca^{2+} release from intracellular stores. The ER is the most important Ca^{2+} store. Its stress, characterized by the impairment of Ca^{2+} homeostasis and by the accumulation of misfolded proteins, can be induced by different factors. In turn, it induces defense mechanisms such as unfolded protein response, and when it is severe and prolonged, activation of the apoptotic pathway. Damage to the ER, impairment of its function, and a decreased level of its Ca^{2+}-handling proteins might all play a role in physiological ageing by handicapping the ER stress response. Thus, healthy ageing is accompanied by subtle alterations of Ca^{2+} homeostasis and signaling, including alterations in the ER Ca^{2+} load and release. The expression and/or function of ryanodine receptors, IP3 receptors, and SERCA Ca^{2+} pumps located in the ER membrane, and Ca^{2+}-binding proteins within ER lumen all seem to be affected in aged cells. Data are presented on age-dependent, tissue-specific changes in ER-related Ca^{2+} homeostasis in skeletal, cardiac and smooth muscles, as well as in the nervous and immune systems. Disturbances of Ca^{2+} homeostasis and of signaling are potential targets for intervention in aged humans.

1. Introduction

1.1. Ca^{2+} transport and storage in brief

Intracellular oscillations in Ca^{2+} ion concentration regulate processes such as proliferation, transcription, contraction, exocytosis, apoptosis, and immune response (reviewed in Carafoli, 2002 and in Berridge et al., 2003). Ca^{2+} concentration is tightly regulated by multiple Ca^{2+} channels, pumps, exchangers and buffers. Eukaryotic cells can increase cytoplasmic Ca^{2+} concentration by influx of these ions through the plasma membrane (PM) and by their release from intracellular stores (Fig. 1). Various Ca^{2+}-permeable channels are present in the PM. In excitable cells, depending on the cell type, voltage-operated Ca^{2+} channels (VOCCs) (reviewed in Bertolino and Llinas, 1992, and in Felix, 2005) or receptor-activated Ca^{2+} channels (RACCs) (reviewed in Trebak et al., 2003) predominate. Transient receptor potential channels (TRPCs) are RACCs that are activated by different stimuli, such as intra- and extracellular messengers, chemical, mechanical, and osmotic stress, and by the Ca^{2+} content of intracellular stores (reviewed in Clapham, 2003). However, RACCs are also present in non-excitable cells, for example, the highly Ca^{2+}-selective arachidonic acid-regulated channels in HEK293, HeLa, COS cell lines and in parotid and pancreatic acinar cells (reviewed in Shuttleworth et al., 2004). Receptor-induced Ca^{2+} signals lead to the release of Ca^{2+} from the endoplasmic reticulum (ER) stores, triggering Ca^{2+} entry through the different PM store-operated channels. Similarly, VOCCs are also expressed in many non-excitable cells (reviewed in Felix, 2005). Highly selective store-operated Ca^{2+} channels (SOCCs) are present in the PM. Since Ca^{2+} regulates numerous and distinct cellular processes, stimulus-evoked Ca^{2+} responses need to be spatially and temporally restricted: Ca^{2+} influx across the PM or its release from the ER creates microdomains with high local

Abbreviations: AD, Alzheimer's disease; APP, amyloid precursor protein; ARC, arachidonic acid-regulated channel; CaMK, calmodulin-dependent protein kinase; CICR, calcium-induced calcium release; Cl_{Ca}, Ca^{2+}-activated Cl^- channel; CRAC, Ca^{2+} release-activated channel; CRU, calcium-release units; DHPR, dihydropyridine receptor; ER, endoplasmic reticulum; IP3, inositol-1,4,5-triphosphate; IP3R, IP3 receptor, Ca^{2+} release channel; JP, junctophilin; K_{Ca}, Ca^{2+}-activated K^+ channel; MG29, mitsugumin29; MI, myocardial infarction; NFAT, nuclear factor of activated T cell; NMDA receptor, *N*-methyl-D-aspartate receptor; Orai1, Ca^{2+} release-activated Ca^{2+} modulator 1; PLB, phospholamban; PM, plasma membrane; PMCA, plasma membrane Ca^{2+}-ATPase; PS1,2, presenilin 1,2; RACC, receptor-activated Ca^{2+} channel; RyR, ryanodine receptor, Ca^{2+} release channel; SERCA, sarco-endoplasmic reticulum Ca^{2+}-ATPase; SLN, sarcolipin; SOCC, store-operated Ca^{2+} channel; SOCE, store-operated Ca^{2+} entry; SR, sarcoplasmic reticulum; STIM1,2, stromal interaction molecule 1,2; TCR, T-cell receptor; TG, thapsigargin; TM, tunicamycin; TPRC, transient receptor potential channel; UPR, unfolded protein response; VOCC, voltage-operated Ca^{2+} channel.

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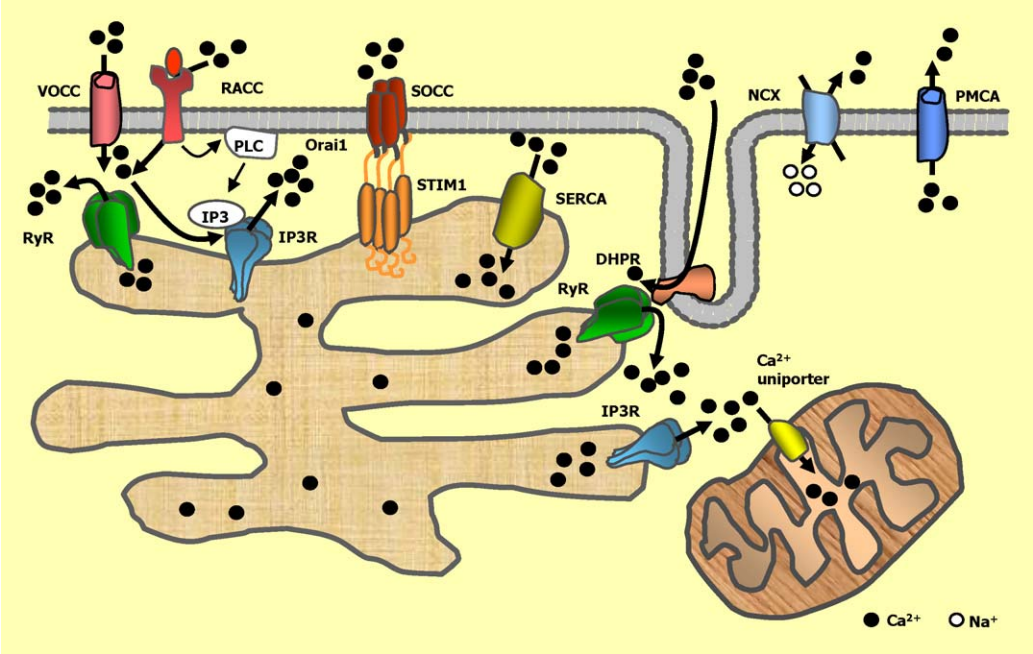

Fig. 1. A simplified model of the ER and ER proteins participating in the maintenance of Ca^{2+} homeostasis and Ca^{2+} signaling.

concentrations of Ca^{2+} (estimated to be in the range of 50–100 μM) (Targos et al., 2005; Kiselyov et al., 2006; McCarron et al., 2006).

The endoplasmic reticulum is an organelle extending throughout all parts of eukaryotic cells. The ER is indispensable for the synthesis, folding, posttranslational modifications and transport of proteins to their target locations (reviewed in Zhang and Kaufman, 2006, and in Görlach et al., 2006). The ER is the most important intracellular Ca^{2+} store that can accumulate Ca^{2+} to concentrations of 10–100 mM, while its concentration in the cytoplasm of the resting cell remains within the range of 100–300 nM (reviewed in Ganitkevich, 2003, in Görlach et al., 2006, and in Rossi et al., 2008). Upon stimulation of PM receptors or upon electrical excitation of the PM, the ER releases Ca^{2+}, thus participating in the generation of rapid Ca^{2+} signals. Since the ER storage capacity is limited, Ca^{2+} release must be followed by Ca^{2+} replenishment. Ca^{2+} movements across the ER membrane are facilitated by three classes of proteins: Ca^{2+} release channels – inositol-1,4,5-triphosphate (IP3) receptors (IP3Rs) (reviewed in Bezprozvanny, 2005 and in Mikoshiba, 2007) and ryanodine receptors (RyRs) (reviewed in Rossi and Sorrentino, 2002, and in Hamilton, 2005), Ca^{2+} re-uptake pumps – sarco-endoplasmic reticulum Ca^{2+}-ATPases (SERCAs) (reviewed in East, 2000 and in Periasamy and Kalyanasundaram, 2007), and luminal Ca^{2+}-binding proteins, such as calsequestrin, sarcalumenin, histidine-rich Ca^{2+}-binding protein, calreticulin, etc.

1.2. The ER and Ca^{2+} handling

IP3Rs, protein components of Ca^{2+} release channels present in the ER membrane, are expressed in all mammalian cells. IP3R contains the IP3-binding suppressor domain, IP3-binding domain, and two putative Ca^{2+}-binding sites in its N-terminal part and in its C-terminal channel-forming domain. There are three isoforms of IP3R (IP3R1–3). The channel is composed of four IP3R subunits (Miyakawa et al., 2001; Bosanac et al., 2002; reviewed in Bezprozvanny, 2005). It releases Ca^{2+} into the cytoplasm in response to IP3 produced by diverse stimuli; however, it is also regulated by other ligands, such as cytoplasmic Ca^{2+} (reviewed in Foskett et al., 2007). RyRs are large proteins positioned in the ER membrane with a major part of their molecules facing the cytoplasm. Transmembrane and luminal domains constitute only approximately 20% of the RyR mass. RyR tetramers form massive Ca^{2+} release channels that interact with many accessory proteins. Ca^{2+}-sensing domains (putative EF-hands) are present on both the luminal and the cytoplasmic sides of RyRs. There are three isoforms of RyR known (RyR1–3). RyR1 and RyR2 are mostly expressed in the skeletal and cardiac muscles, respectively, while RyR3 is expressed ubiquitously. The release of Ca^{2+} from the ER, mediated by RyR channels, is essential for striated muscle contraction and for diverse neuronal functions (Takeshima et al., 1989; reviewed in Hamilton, 2005 and in Laver, 2007). The family of SERCA proteins consists of three isoforms (SERCA1–3) with SERCA2 being evolutionary the oldest and the most widely expressed. In addition, a number of splice variants of these proteins are known: more than 10 different SERCA isoforms have been detected at the protein level (reviewed in East, 2000 and in Periasamy and Kalyanasundaram, 2007). These isoforms exhibit both tissue and temporal specificity. Furthermore, there is evidence showing that different isoforms of SERCA might predominate in various parts of the ER (Liu et al., 2003; Supłat et al., 2004). Their activity is regulated by *N*-glycosylation, glutathionylation, Ca^{2+}/calmodulin kinase II-dependent phosphorylation, and interaction with other proteins such as phospholamban (PLB) and sarcolipin (SLN) expressed in cardiac and skeletal muscles (reviewed in Strehler and Treiman, 2004; Traaseth et al., 2008).

In the majority of excitable cells, a major route of Ca^{2+} entry into the cytoplasm are channels located in the PM; they are different types of VOCCs and RACCs. However, intracellular Ca^{2+} stores, including the ER, also play an important role in signal propagation. A major Ca^{2+} entry pathway in non-excitable cells is initiated by depletion of Ca^{2+} from the ER. In fact, growing body of evidence shows that this mechanism plays an important role in excitable cells, too. Several distinct SOCCs are known including the best-studied Ca^{2+} release-activated channels (CRACs). Concentration of Ca^{2+} in the lumen of the ER is 'sensed' by stromal interaction molecule 1 (STIM1), a protein residing in the ER membrane and containing a single transmembrane domain. Its N-terminus positioned in the lumen of the ER contains the SAM domain, Ca^{2+}-sensing region built of canonical EF-hand, and a 'hidden' EF-hand that does not bind Ca^{2+},