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Review

Intracellular Ca^{2+} storage in health and disease: A dynamic equilibrium

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ABSTRACT

Homeostatic control of the endoplasmic reticulum (ER) both as the site for protein handling (synthesis, folding, trafficking, disaggregation and degradation) and as a Ca^{2+} store is of crucial importance for correct functioning of the cell. Disturbance of the homeostatic control mechanisms leads to a vast array of severe pathologies. The Ca^{2+} content of the ER is a dynamic equilibrium between active uptake via Ca^{2+} pumps and Ca^{2+} release by a number of highly regulated Ca^{2+}-release channels. Regulation of the Ca^{2+}-release channels is very complex and several mechanisms are still poorly understood or controversial. There is increasing evidence that a number of unrelated proteins, either by themselves or in association with other Ca^{2+} channels, can provide additional Ca^{2+}-leak pathways. The ER is a dynamic organelle and changes in its size and components have been described, either as a result of (de)differentiation processes affecting the secretory capacity of cells, or as a result of adaptation mechanisms to diverse stress conditions such as the unfolded protein response and autophagy. In this review we want to give an overview of the current knowledge of the (short-term) regulatory mechanisms that affect Ca^{2+}-release and Ca^{2+}-leak pathways and of the (long-term) adaptations in ER size and capacity. Understanding of the consequences of these mechanisms for cellular Ca^{2+} signaling could provide a huge therapeutic potential.

1. Introduction

Cells dispose of an extensive "tool kit" of proteins to control and fine-tune their Ca^{2+} signaling [1]. As a result, a wide range of Ca^{2+} signals with specific spatio-temporal properties modulates a diversity of cellular processes and intracellular communications, from birth to death [2]. For short-term signaling occurring in seconds or minutes after agonist stimulation, the increase in the free cytoplasmic Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$) has been intensively studied over the years, and the cellular mechanisms responsible for the changes in $[Ca^{2+}]_{cyt}$ are fairly well understood and described in excellent reviews [1,3–8]. One of the major players in Ca^{2+} signaling is the endoplasmic reticulum (ER), which is the largest and most controllable intracellular Ca^{2+} store in non-excitable cells [9,10]. Recently more insight has been obtained in the continuity of the ER lumen as a highway for the distribution of proteins and ions to different regions of the cell [11]. Ca^{2+} tunneling, which is especially important in neurons and pancreatic acinar cells, is an example of this [12–14]. All compartments that have a functional Ca^{2+}-release channel and a pump mechanism to create a favorable electrochemical gradient are essentially capable of acting as specialized Ca^{2+}-release sites [7]. Therefore, other cellular organelles such as mitochondria, the nuclear envelope, the Golgi and lysosomes, which have their own mechanisms for Ca^{2+} uptake and release, add a further level of complexity to Ca^{2+}-signaling events [6,15]. Moreover these different Ca^{2+}-release sites are not independent but in fact there may be close contacts between different organelles as is very well documented between the ER and mitochondria [16,17]. As a result, intra-organellar $[Ca^{2+}]$ changes in the ER or mitochondria directly affect each other. The Ca^{2+} tool kit contains a vast number of "ON" and "OFF" mechanisms, which are subject to a complex set of regulatory feedback systems resulting in a constant remodeling of the Ca^{2+} signalosomes [1]. Recently stromal interaction molecule 2 (STIM2)-activated Ca^{2+} influx upon relatively small decreases in ER $[Ca^{2+}]$ ($[Ca^{2+}]_{ER}$) was found to

Abbreviations: Aβ, amyloid-β; AD, Alzheimer's disease; ADPKD, autosomal dominant polycystic kidney disease; APP, amyloid precursor protein; Bax, Bcl-2-associated Xprotein; BI-1, Bax Inhibitor-1; $[Ca^{2+}]_{cyt}$, cytosolic Ca^{2+} concentration; $[Ca^{2+}]_{ER}$, endoplasmic-reticulum Ca^{2+} concentration; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CICR, Ca^{2+}-induced Ca^{2+} release; CaBP1, Ca^{2+}-binding protein-1; CALHM1, calcium homeostasis modulator 1; CIB, Ca^{2+}- and integrin-binding protein; ER, endoplasmic reticulum; FAD, familial Alzheimer's disease; GAAP, Golgi anti-apoptotic protein; GRP78/BiP, glucose-regulated protein/immunoglobulin heavy chain binding protein; HD, Huntingston's disease; RyR, ryanodine receptor; IP_3, inositol 1,4,5-trisphosphate; IP_3R, inositol 1,4,5-trisphosphate receptor; IICR, IP_3-induced Ca^{2+} release; IRE1α, inositol-requiring enzyme 1α; NAADP, nicotinic acid adenine dinucleotide phosphate; PKA, protein-kinase-A; PKB, protein-kinase-B; SCA, spino-cerebellar ataxia; PS1/2, presenilin1/2; PrP, prion protein; SERCA, sarco-endoplasmic-reticulum Ca^{2+}-ATPase; SR, sarcoplasmic reticulum; SOCE, store-operated Ca^{2+} entry; STIM, stromal interacting molecule; TPC, two-pore channel; TRP, transient receptor potential; TRAF2, tumor necrosis factor receptor (TNFR)-associated factor-2; UPR, unfolded protein response; XBP-1, X-box binding protein-1.

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play a key role in keeping basal $[Ca^{2+}]_{cyt}$ and $[Ca^{2+}]_{ER}$ within tight limits [18]. Among the different mechanisms involved in this dynamic equilibrium, one pathway has remained strikingly enigmatic, i.e. the existence of "basal" Ca^{2+}-leak pathways from the ER that occur in addition to "physiological" Ca^{2+} release, e.g. induced by inositol 1,4,5-trisphosphate (IP_3) [19,20]. Since then, a variety of other ER proteins including the translocon complex, channels of the transient receptor potential (TRP) family-like polycystin-2 (TRPP2), proteins related to neurodegenerative diseases such as presenilins (PS), members of anti-apoptotic proteins of the Bcl2 and Bcl-2-associated Xprotein (Bax)-inhibitor-1 (BI-1) families, hemi-channel-forming proteins such as pannexins, etc., have all been reported to produce an ER Ca^{2+} leak as part of their cellular mechanism. The basal Ca^{2+} leak significantly contributes to the dynamic equilibrium of Ca^{2+} uptake and release that finally determines the ER Ca^{2+} content and downstream effects on ER and mitochondrial function and on the basal $[Ca^{2+}]_{cyt}$ [18].

In addition to the complexity already inherent to acute Ca^{2+} signaling, another level of regulation results from "long-term" adaptations in cellular processes occurring within the time frame of hours and days such as during cell differentiation, proliferation and death. The ER is a very plastic and dynamic organelle and its size and shape can undergo drastic changes to meet changing demands for ER-related functions [21]. Homeostasis of the ER is largely regulated by the unfolded protein response (UPR), which regulates translation and transcription to match increasing demands on the protein-folding capacity [22]. Ca^{2+} signaling is intimately involved in cellular adaptation and remodeling [23–25]. Concomitant changes in the size of the ER Ca^{2+} store and in the expression of intraluminal Ca^{2+}-buffer proteins may therefore be very relevant for shaping the cellular Ca^{2+} signals.

In this review we want to summarize a number of recent findings that pinpoint the ER Ca^{2+} load as a key parameter in Ca^{2+} signaling. We will therefore consider the dynamic equilibrium of Ca^{2+}-uptake and -release pathways with focus on the basal Ca^{2+} leak, as a determinant of acute Ca^{2+} responses. In addition we will refer to recent findings on long-term changes in gene expression and ER remodeling as an important parameter in determining Ca^{2+} signaling during longer time frames.

2. (Un)controlled Ca^{2+} release by classical Ca^{2+}-release channels

Ca^{2+} release from intracellular stores is mainly mediated by two subfamilies of intracellular Ca^{2+}-release channels, IP_3 receptors (IP_3Rs) and ryanodine receptors (RyRs), which are both represented by three different genes encoding three different isoforms [1]. These two channel families differ in expression profiles, cellular localization, function, and activation mechanism. IP_3Rs are activated downstream of the formation of IP_3 as a consequence of activation of plasma-membrane receptors. RyRs are activated downstream of membrane depolarization either by direct coupling to plasma-membrane voltage-dependent Ca^{2+} channels or by Ca^{2+}-induced Ca^{2+} release (CICR) subsequent to Ca^{2+} influx via these voltage-dependent Ca^{2+} channels. A detailed description of the activation and regulation of IP_3Rs [26–32] and RyRs [33–35] has been given in several excellent reviews. For both families of intracellular Ca^{2+} channels the store Ca^{2+} content has been widely documented to be a key modulator of Ca^{2+} release [36–42]. Different mechanisms have been proposed to explain the effect of the store Ca^{2+} content on the magnitude of the Ca^{2+} signal including luminal and cytosolic Ca^{2+}-sensor sites regulating the activity of the release channel. The question then arises whether in some conditions a "Ca^{2+}-leak" pathway via the Ca^{2+}-release channel itself could contribute to the steady-state level of the luminal $[Ca^{2+}]$ and thereby to the regulation of the Ca^{2+} release in physiological or pathological conditions [43]. It should be pointed out that besides the intracellular Ca^{2+} channels, also the Ca^{2+} uptake into the ER by sarco-endoplasmic-reticulum Ca^{2+}-ATPases (SERCA) is regulated by the store Ca^{2+} content. This SERCA activity allows for the rapid termination of a cytosolic Ca^{2+} signal [44,45]. In this review we will not discuss these effects on Ca^{2+} pumps in more detail. We will mainly focus on Ca^{2+} release via the IP_3R and in addition we will discuss the RyR and the recently discovered two-pore channels (TPC), which represent until now the only three Ca^{2+}-release pathways for which coupling to physiological signaling is documented.

2.1. Ca^{2+} release via IP_3R channels

IP_3Rs are gated in a complex way by IP_3 and Ca^{2+} [46], which is in agreement with structural properties of their amino-terminal region [47–50]. There are however persistent indications for the occurrence of IP_3R leak pathways or malfunctions deviating from normal IP_3-induced gating [43]. The regulatory domain of the IP_3R is necessary to maintain the channel closed [51]. A Ca^{2+}-leak activity has been proposed for the truncated C-terminal channel domain of the IP_3R1 that is formed by caspase-3 cleavage of IP_3R1 during apoptosis, which may contribute to a late apoptotic phenotype [52–54]. However, a dead-channel mutant of the C-terminal domain evoked similar anti-apoptotic effects, and therefore the role in apoptosis was questioned [55,56]. Gating of the IP_3R was found to depend on critical regions in the N-terminal domain and a five-domain structure model was proposed to explain coupling to the C-terminal tail, which acts as a gatekeeper [57]. Mechanical transmission of IP_3-induced conformational changes was proposed to occur through an attachment to the S4-S5 linker in the channel domain [58] and mutagenesis data revealed critical residues in the channel domain [59]. It is conceivable that mimicking the proper protein interactions could activate channel opening even in the absence of IP_3 as was demonstrated by targeted expression of the all-helical portion of the IP_3R ligand-binding domain [60].

The IP_3R is a substrate for many protein kinases, and phosphorylation can regulate its activity either directly or indirectly by changing the ER Ca^{2+} content [31]. Hyperphosphorylation of the IP_3R1 at a protein-kinase-A (PKA) site, a condition believed to increase IP_3R activity [61], was found to decrease the $[Ca^{2+}]_{ER}$ [62] (Fig. 1). Down-regulation with RNAi demonstrated the involvement of IP_3R1 in the Ca^{2+} leak, but it is not entirely clear if this involvement implies an IP_3-independent leak or a hypersensitivity to basal levels of IP_3. The condition of hyperphosphorylation is particularly important for the role of IP_3Rs in apoptosis. The data suggest that the ratio of pro- to anti-apoptotic Bcl2-family members regulates the phosphorylation status of the IP_3R1 and thereby the Ca^{2+} leak and the $[Ca^{2+}]_{ER}$ [62]. This regulation of $[Ca^{2+}]_{ER}$ by Bcl2-family members constitutes a control point for apoptotic death in response to agents that release Ca^{2+} from intracellular stores [63]. Central to this model is the close apposition of mitochondrial and ER Ca^{2+}-release sites that allows rapid accumulation of Ca^{2+} in the mitochondrial matrix [6,16] (Fig. 1). Although there is consensus in the literature on the direct interaction between the IP_3R and either Bcl2 and BclXL, the mechanism(s) responsible for the resulting effects on Ca^{2+} release from the ER are still controversial [64–67]. On the one hand there are several groups that find an increased Ca^{2+} leak and consequently a decreased $[Ca^{2+}]_{ER}$, which would limit the amount of Ca^{2+} that can be released (reviewed in [68]); on the other hand there is evidence that Bcl2 directly inhibits IP_3-induced Ca^{2+} release (IICR) without a concomitant change in the $[Ca^{2+}]_{ER}$ [69–72]. In addition, for BclXL a direct interaction with the C-terminal part of the IP_3R sensitized single channels to a low $[IP_3]$ suggesting a model where BclXL protects cells against apoptosis by a more dynamic coupling of ER to mitochondria that enhances cellular bioenergetics and preserves