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Review

The endoplasmic reticulum and junctional membrane communication during calcium signaling☆

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ABSTRACT

The endoplasmic reticulum is a major organelle in all eukaryotic cells which performs multiple functions including protein and lipid synthesis and sorting, drug metabolism, and Ca^{2+} storage and release. The endoplasmic reticulum, and its specialized muscle counterpart the sarcoplasmic reticulum, is the largest and most extensive of Ca^{2+} storage organelle in eukaryotic cells, often occupying in excess of 10% of the cell volume. There are three major components of Ca^{2+} storage organelles which mediate their major functions: Ca^{2+} uptake, mediated by pumps and exchangers; storage enhanced by luminal Ca^{2+} binding proteins, and Ca^{2+} mobilization mediated by specific ion channels. Ca^{2+} mobilization from the endoplasmic reticulum plays a central role in Ca^{2+} signaling. Through Ca^{2+} release channels in its membrane, the pervading and plastic structure of the endoplasmic reticulum allows Ca^{2+} release to be rapidly targeted to specific cytoplasmic sites across the whole cell. That several endoplasmic reticulum Ca^{2+} release channels are also activated by Ca^{2+} itself, contributes to endoplasmic reticulum membrane excitability which is the principal basis for generating spatio-temporal complex cellular Ca^{2+} signals, allowing specific processes to be regulated by this universal messenger. In addition, the endoplasmic reticulum forms discrete junctions with the plasma membrane and membranes of organelles such as mitochondria and lysosomes, forming nanodomains at their interfaces that play critical roles in Ca^{2+} signaling during key cellular processes such as cellular bioenergetics, apoptosis and autophagy. At these junctions key Ca^{2+} transport and regulatory processes come into play, and a recurring theme in this review is the often tortuous paths in identifying these mechanisms unequivocally. This article is part of a Special Issue entitled: Functional and structural diversity of endoplasmic reticulum.

1. Introduction

Ca^{2+} ions are the most commonly employed signal transduction element in intracellular signaling [1]. In contrast with other intracellular messengers, Ca^{2+} is neither synthesized or metabolized. Instead its storage and circulation are controlled in cells by the regulation of channels, pumps and exchangers, which act to determine spatially and temporally the precise concentrations in the cytoplasm and other cellular compartments. Ca^{2+} ions are highly buffered in the cytoplasm, with individual free Ca^{2+} ions on average diffusing less than 1 μm over a few μs before being captured by binding proteins or translocated by pumps or transporters [2]. Ca^{2+} ions are thus inherently highly localized messengers, and Ca^{2+} entry across the plasma membrane will only affect sub-plasma membrane targets. In contrast, Ca^{2+} storage organelles may be positioned throughout the cell to target Ca^{2+} precisely to cytoplasmic Ca^{2+} effector proteins throughout the cell. It is important to consider Ca^{2+} changes on both sides of the organellar membrane. Increased Ca^{2+} loading of stores may itself be an important luminal trigger for opening of Ca^{2+} release channels from within [3]. Release of Ca^{2+} into the cytoplasm from the ER will also lower luminal Ca^{2+} concentrations and this is in itself a signal for capacitative calcium entry, and may modulate the other major functions of the ER given its multi-tasking roles in protein synthesis and folding, at least over prolonged periods of Ca^{2+} signaling [4]. Chronic ER Ca^{2+} depletion, for example, in Darier's disease due to mutations in SERCA2a pumps, results in abnormalities in protein synthesis and targeting in keratinocytes which rely exclusively on this pump isoform [5].

The ER plays a central role in cellular Ca^{2+} homeostasis and signaling. First it acts as an important component of the cell's Ca^{2+} buffering systems, which act to maintain cytoplasmic free Ca^{2+} concentrations at extremely low levels, typically around 100 nM. Ca^{2+} pumps and exchangers in the ER membrane are critical for this role, which allow the sequestration of Ca^{2+} into the lumen yielding luminal free Ca^{2+} concentrations as high as 100–500 μM, as direct measurements using luminally-targeted Ca^{2+} probes have indicated. This role was first discovered over fifty years ago, when vesicles of fragmented SR were found to cause the relaxation of permeabilized muscle fibers through ATP-dependent Ca^{2+} uptake [6]. Some years later, the family of proteins

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responsible, the sarco-endoplasmic reticulum Ca^{2+} ATPases (SERCA pumps) were purified, sequenced and cloned [7]. They were found to be inhibited by the plant sesquiterpene lactone, thapsigargin, which has been a major tool in the study of ER Ca^{2+} storage and the consequences of perturbing it [8]. The role of the SR/ER as a source of Ca^{2+} signals in cellular processes was again led by studies of striated muscle, with the discovery of Ca^{2+}-induced Ca^{2+} release (CICR) from the SR [9,10]. The role of the ER as a source of Ca^{2+} for cell signaling was noted with the finding that intracellular pools of Ca^{2+} play a major role in stimulus-secretion coupling in exocrine glands [11]. This was extended with the discovery that inositol 1,4,5 trisphosphate (IP_3) mobilized Ca^{2+} from non-mitochondrial stores in permeabilized pancreatic acinar cells [12], and the identification of specific IP_3-gated calcium channels (IP_3 receptors, IP_3Rs) expressed in ER membranes [13].

Studies on the Ca^{2+} release channels of the ER, showed that IP_3Rs in common with RyRs are also activated by Ca^{2+} in addition to IP_3 [14], and that RyRs can be activated by another Ca^{2+} mobilizing intracellular messenger, cyclic ADP-ribose (cADPR) [15]. These messengers serve to modulate the process of CICR mediated by these intracellular channels, allowing the ER network to function as an excitable system displaying regenerative propagating cytoplasmic Ca^{2+} waves. For this reason, the ER, when discussed in terms of neuronal Ca^{2+} signaling, has been termed a "neuron within a neuron' [16], with the chemical excitability of this intracellular membrane network showing several striking parallels with the electrical excitability of the neuronal plasma membrane. Indeed, isolated SR vesicles, when reconstituted into an agarose matrix, can be demonstrated to support regenerative Ca^{2+} waves [17]. This analogy can be further extended with the nervous system by using the term "Ca^{2+} synapses" to describe the close appositions of ER regions with either the plasma membrane or organelles such as mitochondria or lysosomes. Such ER junctions, sites of Ca^{2+} transfer, are emerging as key intracellular microdomains for Ca^{2+} signaling [18] (Fig. 1). They are now considered crucial for generating, coordinating and integrating intracellular Ca^{2+} signals which are a major focus of this review article, along with the molecular components of Ca^{2+} and ion signaling, which are often concentrated at these sites.

2. Morphology and architecture of the ER

The ER was described and named by Keith Porter in his pioneering studies of cell ultrastructure by the then emerging technique of electron microscopy in the 1940s and 1950s [19]. Given the multifarious roles of the ER in cells, the size of this organelle varies between cells depending on their specializations. In terms of its role in Ca^{2+} signaling, it was perhaps not surprising that studies of striated muscle led the way, with the SR, given its specialized role in excitation–contraction coupling, identified as Ca^{2+}-accumulating structures in skeletal muscle by visualizing calcium oxalate accumulation by electron microscopy [20].

2.1. Structure and heterogeneity of Ca^{2+} stores

The ER is a continuous membranous network with distinct morphologies in all nucleated eukaryotic cells. In the case of rough ER, which is particularly well developed in cells that secrete proteins, it appears as flattened sacs or cisternae, where membranes are studded with ribosomes at sites of protein synthesis of integral membrane proteins or those destined for vesicular trafficking including exocytosis. Smooth ER often appears as comprised of more tubular structures, and is a site of lipid synthesis, and plays a major role in Ca^{2+} storage and release. The nuclear envelope is contiguous with the ER, but may also act as a discrete Ca^{2+} store in the perinuclear region of the cell. Under physiological conditions, the ER network has been shown to be a continuous structure [21,22], and may function as a connected Ca^{2+} store. In a series of elegant experiments, Petersen and colleagues showed that Ca^{2+} diffuses more rapidly in the ER lumen of pancreatic acinar cells than it does in the cytoplasm on account of lower luminal buffering. Taking advantage of the polarized nature of acinar cells, they showed that Ca^{2+} uptake by the ER in the basolateral domain could refill fingers of ER in the secretory pole via a lumen rather than a cytoplasmic route, a process they termed "tunneling" [23]. However, functionally in some cells the ER may operate as a series of discrete heterogeneous Ca^{2+} stores. Heterogeneity of the ER in terms of Ca^{2+} signaling is due to the spatial distribution

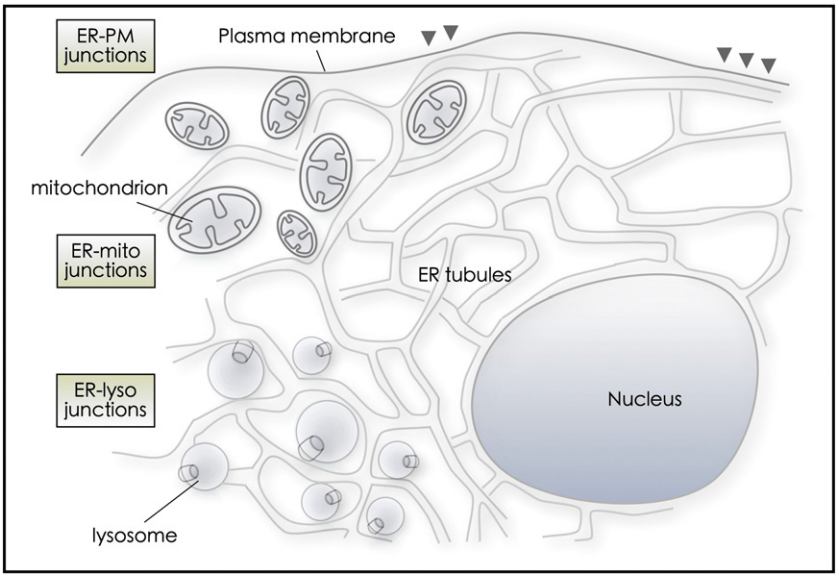

Fig. 1. The ER and junctional membrane communication during Ca^{2+} signaling. Schematic depicting the nanometer-scale junctions formed between the ER and the plasma membrane, mitochondria and lysosomes. The elaborated tubular system of the ER allows multiple parallel, dynamic interactions with organellar membranes, allowing for real-time information exchange using Ca^{2+} as a signaling messenger. The emerging view is that the ER processes and integrates the multiple inputs from various interacting organelles to elicit a resultant Ca^{2+} response of a particular phenotype which may also be modulated in real-time. Supporting this view, loss or malfunction of any of the organellar inputs can result in defects in eliciting the 'intended' or 'default' Ca^{2+} phenotype. For example, Ca^{2+} oscillations ('default') are switched to a sustained low amplitude Ca^{2+} elevation when mitochondrial Ca^{2+} release is inhibited [56] or complete cessation of oscillatory Ca^{2+} transients when SOCE is inhibited [148].