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Fundamentals of Cellular Calcium Signaling: A Primer

Martin D. Bootman¹ and Geert Bultynck²

¹School of Life, Health and Chemical Sciences, The Open University, Milton Keynes MK7 6AA, United Kingdom

²Laboratory of Molecular and Cellular Signaling, Department of Cellular and Molecular Medicine, KU Leuven, B-3000 Leuven, Belgium

Correspondence: martin.bootman@open.ac.uk

Ionized calcium (Ca^{2+}) is the most versatile cellular messenger. All cells use Ca^{2+} signals to regulate their activities in response to extrinsic and intrinsic stimuli. Alterations in cellular Ca^{2+} signaling and/or Ca^{2+} homeostasis can subvert physiological processes into driving pathological outcomes. Imaging of living cells over the past decades has demonstrated that Ca^{2+} signals encode information in their frequency, kinetics, amplitude, and spatial extent. These parameters alter depending on the type and intensity of stimulation, and cellular context. Moreover, it is evident that different cell types produce widely varying Ca^{2+} signals, with properties that suit their physiological functions. This primer discusses basic principles and mechanisms underlying cellular Ca^{2+} signaling and Ca^{2+} homeostasis. Consequently, we have cited some historical articles in addition to more recent findings. A brief summary of the core features of cellular Ca^{2+} signaling is provided, with particular focus on Ca^{2+} stores and Ca^{2+} transport across cellular membranes, as well as mechanisms by which Ca^{2+} signals activate downstream effector systems.

GENERAL PRINCIPLES OF CELLULAR Ca^{2+} SIGNALING

A key principle of Ca^{2+} signaling is that a change of the intracellular Ca^{2+} concentration provokes a cellular response (Berridge et al. 2000). In unstimulated cells, the cytosolic Ca^{2+} concentration is maintained at ~ 100 nM (often referred to in the Ca^{2+} signaling literature as the “resting” or “basal” Ca^{2+} concentration). Extrinsic stimulation of cells can take many forms—hormonal, neurotransmitter, growth factor, antibody, mechanical, electrical, gasotransmitter, temperature, pH change, osmotic change,

cytotoxic reagents, microbial invasion, and gap junction-mediated passage of cellular signals—all of which have been shown to elevate cytosolic Ca^{2+} concentration. Alternatively, Ca^{2+} signaling can occur because of intrinsic cellular cues, such as the spontaneous Ca^{2+} signals within cardiac myocytes (Hüser et al. 2000) and developing neurons (Ciccolini et al. 2003).

Typically, stimulation of cells leads to an acute increase in cytosolic Ca^{2+} concentration from the resting level of 100 nM, and at the end of stimulation the Ca^{2+} concentration returns back to the resting state. The level of cytosolic Ca^{2+} attained depends on the nature of the

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stimulus, as well as factors such as the concentration, intensity and duration of the stimulus, and presence of Ca^{2+} -buffering proteins (Schwaller 2010) and respiring mitochondria (Wacquier et al. 2019). If the cytosolic Ca^{2+} concentration is monitored by taking an average measure across a whole cell, as is often done using Ca^{2+} -sensitive fluorescent indicators such as Fura-2 (Bootman et al. 2013), Ca^{2+} signals typically reach peak levels of 0.5–1 μM (Fig. 1).

Averaged cytosolic Ca^{2+} signals $>1 \mu\text{M}$ have been recorded, but such large elevations of Ca^{2+} concentration require a substantial movement of Ca^{2+} into the cytosol to counteract the energy-dependent homeostatic Ca^{2+} clearance mechanisms employed by cells. Such excessive Ca^{2+} signals are often caused by cellular damage, and are generally considered to be in a non-physiological range. Large elevations of cytosolic Ca^{2+} concentration can lead to a variety of deleterious cellular effects, particularly if they are sustained for minutes, because of the activation of Ca^{2+} -dependent proteases, production of reactive oxygen species, acute organelle remodeling, and mitochondrial permeability transition (Orrenius et al. 2003). Examples of the dis-

astrous cellular effects of large Ca^{2+} elevations include excitotoxic stimulation of neurons (Vergun et al. 1999) and death of vascular smooth muscle cells exposed to naturally occurring calcified particles (Proudfoot 2019). However, it is not only large elevations of Ca^{2+} concentration that are linked to poor cellular outcomes. Indeed, Ca^{2+} is implicated in numerous pathologies (Parys and Bultynck 2018) as well as in processes underlying natural aging (Verkhatsky 2019). In many cases, subtle alterations of Ca^{2+} signaling mediate functional or phenotypic changes (Berridge 2012, 2017). The discussion above alludes to the precarious position of cells with regard to Ca^{2+} signaling. On one hand, Ca^{2+} is a dynamic and versatile signal within cells, whereby the chemistry of Ca^{2+} makes it more suitable than other ions for this purpose (Clapham 2007). On the other hand, too much, too little, or misappropriate Ca^{2+} signaling will ultimately affect cell behavior and fate (Mekahli et al. 2011; Giorgi et al. 2018a).

Understanding the principles underlying Ca^{2+} dynamics in health and their perturbation in disease and aging also presents unique opportunities to develop strategies to restore normal

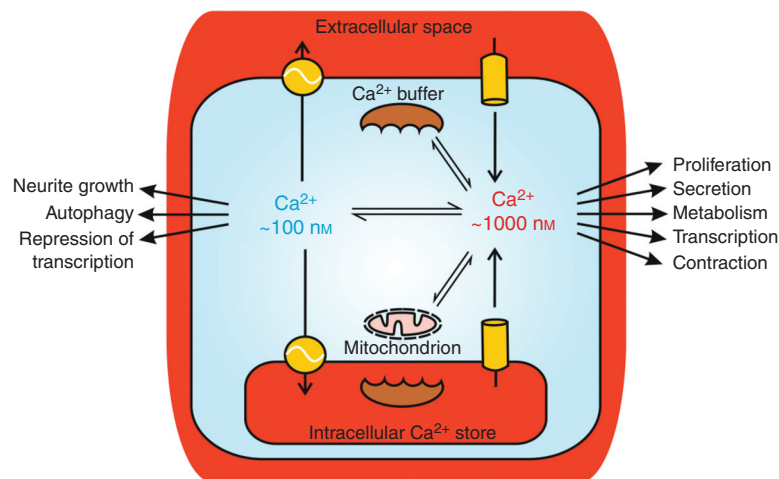


Figure 1. Cytosolic Ca^{2+} signals arise via Ca^{2+} release from intracellular organelles and/or Ca^{2+} influx across the plasma membrane. During physiological Ca^{2+} signaling, the averaged cytosolic Ca^{2+} concentration typically increases from $\sim 100 \text{ nM}$ to $\sim 1 \mu\text{M}$, depending on the stimulus and factors such as buffering of Ca^{2+} by mitochondria and Ca^{2+} -binding proteins. Cellular processes are specifically switched on or off when the cytosolic Ca^{2+} concentration is altered. The main intracellular Ca^{2+} store is the endoplasmic reticulum (ER), but also the nuclear envelope, Golgi, and acidic compartments such as lysosomes function as Ca^{2+} stores (see text).



cell function, which is a central theme in regenerative medicine. Therefore, researchers have turned their focus on studying Ca^{2+} signaling in regeneration, for example, using organisms and model systems with a powerful inherent regenerative capacity, such as planarian flatworms (Marchant 2019).

Ca^{2+} is often regarded as a signal when its cytosolic concentration is elevated. Indeed, Ca^{2+} has many dramatic effects within cells when its concentration is increased. However, it is important to remember that the absence of Ca^{2+} elevation (i.e., the resting Ca^{2+} concentration), may also have a signaling function because some processes within cells are inhibited by an elevation of cytosolic Ca^{2+} concentration. For example, the transcriptional repressor downstream regulatory element antagonist modulator (DREAM) binds to target genes and prevents their transcription at resting Ca^{2+} concentration (Hagenson et al. 2019). In addition, neurite outgrowth has been negatively correlated with Ca^{2+} signaling in some neuronal cell types (Mattson et al. 1988). A lack of Ca^{2+} signaling can trigger processes such as quiescence (a reversible growth/proliferation arrest) (Humeau et al. 2018) or autophagy, a lysosomal turnover pathway responsible for the clearance of damaged or unwanted proteins and organelles (Bootman et al. 2018). Consequently, it should be remembered that Ca^{2+} signals have pleiotropic actions within cells: some processes will be switched on, while others are switched off, when the cytosolic Ca^{2+} concentration is elevated. The cellular effect of Ca^{2+} signaling also depends on the context of a cell in terms of its position in the cell cycle, energetic status, and other incoming external signaling cues. All of the above paints a complex picture of cellular responses to stimuli that evoke cytosolic Ca^{2+} signals. Indeed, it is this complexity, coupled with a desire to understand how specific cell types generate their individualistic Ca^{2+} signals, which sustains the interest of the many laboratories around the world who study signal transduction by Ca^{2+} .

Cells can access two principal sources of Ca^{2+} to generate signals: Ca^{2+} release from intracellular stores and Ca^{2+} influx from the extracellular space (Fig. 1). Both of these Ca^{2+} sources

are utilized by cells, but the balance between the two can differ. For example, cytosolic Ca^{2+} signals mediate contraction of both skeletal and cardiac muscle by activating the engagement of actin and myosin fibers (Santulli et al. 2017). However, skeletal muscle cells can continue to contract for some time in the absence of extracellular Ca^{2+} , whereas cardiac muscle cells will immediately cease contracting if extracellular Ca^{2+} is withdrawn (Eisner et al. 2017).

Ca^{2+} release from intracellular stores occurs via channels that span the membranes of organelles. Principal Ca^{2+} releasing channels are inositol 1,4,5-trisphosphate receptors (IP_3Rs) (Prole and Taylor 2019), ryanodine receptors (RyRs) (Lanner et al. 2010), two-pore channels (TPCs) (Galione 2019; Lloyd-Evans and Waller-Evans 2019; Webb et al. 2019), and the mucolipin subfamily of transient receptor potential channels (TRPML) (Vangeel and Voets 2019). The endoplasmic reticulum (ER) in nonexcitable cells and neurons, and the sarcoplasmic reticulum (SR) in muscle cells, have long been known as major intracellular Ca^{2+} stores that play roles in cellular Ca^{2+} signaling. However, other organelles—the Golgi, nuclear envelope, lysosomes, and other acidic vesicles—also participate in cellular Ca^{2+} signals when cells are appropriately stimulated (Fig. 2). These Ca^{2+} stores contain substantial amounts of Ca^{2+} through the expression of various Ca^{2+} transporters (Vandecaetsbeek et al. 2011; Chen et al. 2019; Lloyd-Evans and Waller-Evans 2019) and a range of Ca^{2+} -binding proteins (Wang et al. 2019). Other organelles, notably mitochondria and peroxisomes, also play roles in intracellular Ca^{2+} signaling, but are not substantial constitutive Ca^{2+} stores. Both mitochondria and peroxisomes sequester Ca^{2+} during cytosolic Ca^{2+} increases. The accumulation of Ca^{2+} by these organelles serves to limit the amplitude of cytosolic Ca^{2+} signals, just as cytosolic Ca^{2+} -binding proteins do (Fig. 1; Schwaller 2019; Wacquier et al. 2019). However, the role of these compartments is not just to dampen cytosolic Ca^{2+} rises. For instance, the uptake of Ca^{2+} by mitochondria intimately links cellular signaling to metabolism and bioenergetics (Cárdenas et al. 2010) and cell fate (Walter and Hajnóczky 2005). In

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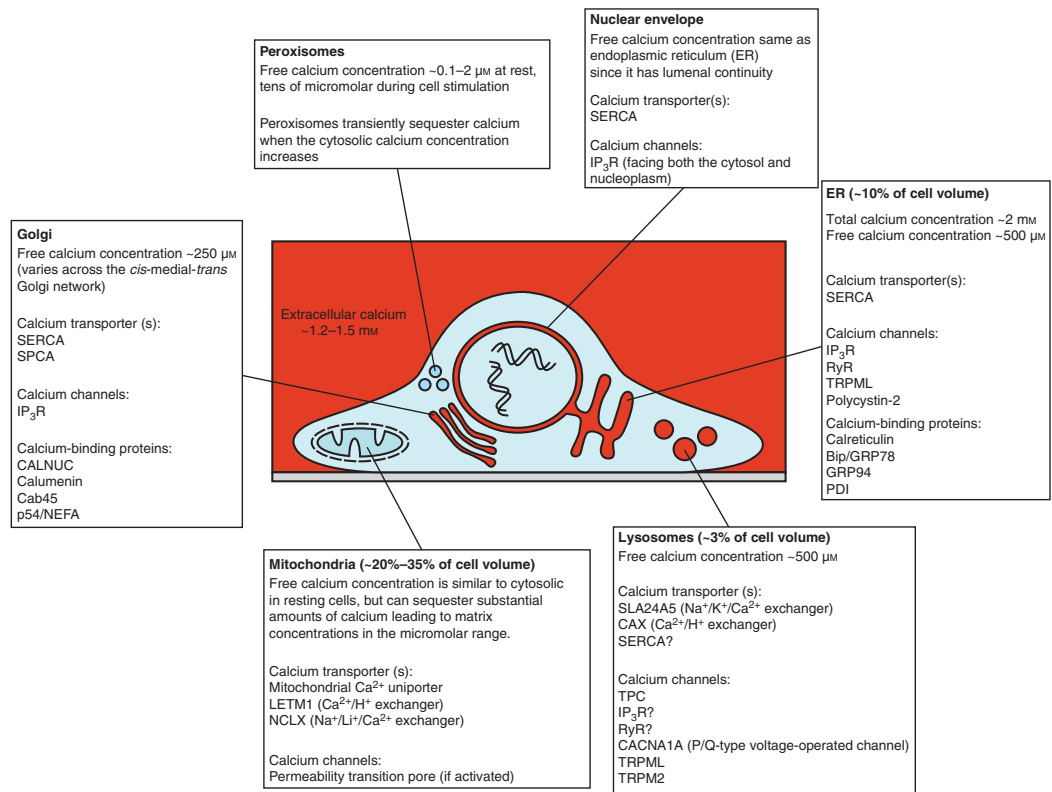


Figure 2. Ca²⁺-sequestering organelles. Cellular Ca²⁺ signaling involves combinations of organelles depending on the tissue type and stimulus. Although there is considerable overlap in some of the organelles' characteristics, they also have discrete properties that imbue each of the organelles with the ability to generate distinctive Ca²⁺ signals. Mitochondria and peroxisomes are not constitutive Ca²⁺ stores, but have the capacity to sequester Ca²⁺ during cytosolic Ca²⁺ increases. For more details, see Wang et al. (2019), Chen et al. (2019), Lloyd-Evans and Waller-Evans (2019), Wacquier et al. (2019), and Vangeel and Voets (2019). A significant Ca²⁺ store not shown in the figures is the sarcoplasmic reticulum (SR), which plays a critical Ca²⁺ signaling role in muscle cells. For details about SR function and Ca²⁺ homeostasis see Wang et al. (2019) and Gilbert et al. (2019). SERCA, sarcoendoplasmic reticulum Ca²⁺-ATPase; SPCA, Golgi/secretory pathway Ca²⁺ ATPase; TPC, two-pore channel; IP₃R, inositol 1,4,5-trisphosphate receptor; RyR, ryanodine receptor.

the mitochondrial matrix, Ca²⁺ is a cofactor for some enzymes within the tricarboxylic acid cycle, and promotes ATP production, but can also trigger release of proapoptotic factors (Giorgi et al. 2018b). Moreover, not only does Ca²⁺ impact mitochondrial metabolism, but mitochondrial metabolism also boosts cellular Ca²⁺ signaling through regulation of cytosolic Ca²⁺ signals and redox signaling (Booth et al. 2016; Joseph et al. 2019).

Although organelles may contain sufficient Ca²⁺ to initiate and sustain signaling for minutes, they are finite Ca²⁺ stores and will run

down if not replenished. Ultimately, Ca²⁺ from the extracellular space is required to renew organellar Ca²⁺ and prolong cytosolic Ca²⁺ signals. However, it should be noted that extracellular Ca²⁺ can also function to trigger the release of Ca²⁺ from intracellular stores, as happens in cardiac myocytes (Gilbert et al. 2019), and can directly activate downstream effectors, as happens in neurons (Barak and Parekh 2019; Burgoyne et al. 2019; Hagenston et al. 2019). Indeed, Ca²⁺ signals arising from organellar Ca²⁺ release or from Ca²⁺ influx can have discrete cellular outcomes (Barak and Parekh 2019).

A Ca^{2+} SIGNALING TOOLKIT

A simple paradigm that rationalizes the enormous number of components that cells express to generate Ca^{2+} signals, and respond to them, is that of a toolkit (Berridge et al. 2000). The “ Ca^{2+} signaling toolkit” is essentially all the Ca^{2+} transporters (channels, pumps, and exchangers), Ca^{2+} -binding proteins, and Ca^{2+} -dependent effectors that exist in nature. From this vast toolkit, cells express the components that fit their function. For example, cardiac myocytes express a specific set of proteins—voltage-operated Ca^{2+} channels, RyRs, sodium-calcium exchangers, SERCA2a, and troponin C—that enable them to generate Ca^{2+} signals that rise and recover within tens of milliseconds, and so trigger pulsatile cellular contraction to pump blood (Bers 2008; Fearnley et al. 2011). In the average human lifetime, cardiac myocytes beat over 2 billion times, and are activated every second by an action potential arriving from the sinoatrial node, so they need to have the ability to rapidly respond and recover with great fidelity. Missing a beat is not an option! In contrast, oocytes are largely dormant cells, waiting for sperm to trigger Ca^{2+} signaling, cause resumption of the cell cycle, and initiate development (Wakai et al. 2019). Mammalian oocytes express different components from the Ca^{2+} signaling toolkit— IP_3 Rs and SERCA2b—and following fertilization they display a series of long-lasting Ca^{2+} oscillations with much slower kinetics than the rapid Ca^{2+} transients observed in cardiomyocytes. Elucidating the specific Ca^{2+} signaling toolkit components that are discretely expressed by each tissue type, and how they collectively shape Ca^{2+} signal generation and cellular outcomes, is the key to understanding signal transduction via Ca^{2+} .

It is important to note that the Ca^{2+} signaling components expressed by cells can be remodeled because of environmental factors or genetic mutation. A well-known example occurs during hypertrophic growth of cardiac myocytes. Hypertrophic stimuli cause an increase in the amplitude of cytosolic Ca^{2+} signals and larger myocyte contraction (Harzheim et al. 2009), which is a necessary compensation for

greater hemodynamic demand, for example, during pregnancy or athletic training. However, in some deleterious situations (e.g., hypertension) hypertrophy can progress to a maladapted state in which Ca^{2+} signals are reduced, and the heart becomes weaker (Roderick et al. 2007). Moreover, the altered expression or mutation of the Ca^{2+} signaling toolkit components can lead to oncogenesis and malignant cellular behavior, as is observed in several cancer types (Distelhorst and Bootman 2019; Roberts-Thomson et al. 2019).

IP_3 RS AS AN EXAMPLE OF A CELLULAR SIGNALING HUB

There are too many components in the Ca^{2+} signaling toolkit to describe in this limited primer, but some elements are so widely expressed and commonly involved in the generation of Ca^{2+} signals that they deserve a mention. In particular, IP_3 Rs, which are a principal means of releasing Ca^{2+} from intracellular organelles, participate in Ca^{2+} signaling within many excitable and nonexcitable cell types (Foskett et al. 2007; Mikoshiba 2015). IP_3 Rs are activated following the production of the intracellular messenger IP_3 and release Ca^{2+} from the ER, Golgi, and nuclear envelope (Prole and Taylor 2019), as well as activating a small number of IP_3 Rs that are localized at the plasma membrane (Dellis et al. 2006). IP_3 production within cells is triggered by a variety of extrinsic stimuli (e.g., hormones, growth factors) that bind to cell-surface receptors (e.g., G-protein-coupled receptors or receptor tyrosine kinases). Application of these stimuli typically induces Ca^{2+} signals inside cells within a few seconds (Berridge and Galione 1988). As with many components of the Ca^{2+} signaling toolkit, IP_3 -mediated Ca^{2+} release is far from simply being a discrete linear pathway. Indeed, the phosphoinositide signaling pathway (a name commonly used to denote the production of IP_3 and activation of IP_3 Rs within cells) is at the center of a web of interactions with other signaling pathways. Phospholipase C (PLC), the enzyme that produces IP_3 inside cells (via the hydrolysis of the minor membrane phospholipid phosphatidylinositol 4,5-bisphosphate

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[PIP₂]), is expressed as several isoforms, and only some (e.g., PLC-β, PLC-γ) are activated by extrinsic stimuli. Other isoforms are activated by Ca²⁺ (most PLCs, but especially PLC-δ and PLC-η), the small G-protein Ras (PLC-ε), or introduced into oocytes by sperm at fertilization (PLC-ζ) (Fig. 3). Besides producing IP₃, the hydrolysis of PIP₂ by PLC yields diacylglycerol (DAG) that stays within the plasma membrane. DAG can activate protein kinase C (often in cooperation with Ca²⁺ signals) (Lipp and Reither 2011) or can be further metabolized to produce additional cellular messengers such as arachidonic acid.

Profound insights into the activation of IP₃Rs have been gained via high-resolution structural studies using cryo-electron microscopy (cryo-EM), a major tour de force given the large size of IP₃R proteins (IP₃Rs are tetramers of ~270 kDa subunits, giving functional channels of ~1100 kDa) (Fan et al. 2015, 2018; Hamada et al. 2017). Cryo-EM allows the deter-

mination of a protein's structure without requiring its crystallization, an advantage compared to X-ray crystallography or nuclear magnetic resonance spectroscopy, since crystallization is particularly challenging for large, membranous proteins. The structural organization of IP₃R is further discussed in Ivanova et al. (2019).

IP₃Rs are known to bind a range of accessory proteins, many of which convey messages to and from other signaling pathways (Prole and Taylor 2019). Some of the accessory proteins associated with IP₃Rs affect channel opening and Ca²⁺ release, while others determine IP₃R degradation, cellular location, or serve to tether additional proteins that do not directly impact on IP₃R function. An emerging class of IP₃R-associated proteins is the Bcl-2 family, which are critical controllers of apoptotic cell death (Vervliet et al. 2016; Ivanova et al. 2019). As the expression of Bcl-2-family members is altered in cancer, such IP₃R/Bcl-2-protein complexes form a mechanistic link between Ca²⁺ signaling and cell

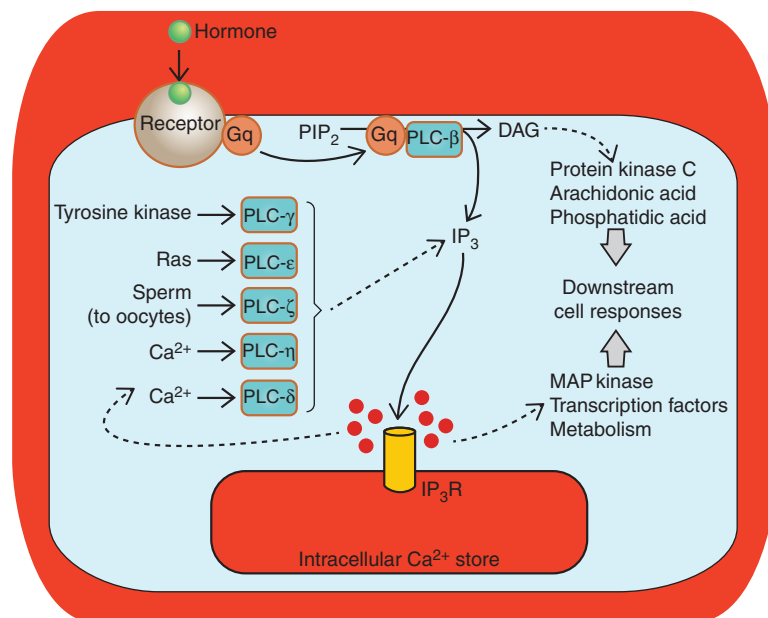


Figure 3. IP₃-mediated Ca²⁺ release is a common outcome from a number of cellular signaling processes and evokes a range of downstream outcomes. A generic pathway leading from hormone-receptor activation, activation of a heterotrimeric G-protein (Gq) and phospholipase C β (PLC-β) is depicted centrally. However, the other PLC isoforms provide alternative mechanisms for activating Ca²⁺ signaling via IP₃Rs. (From Bootman et al. 2009; adapted, with permission, from Company of Biologists © 2009.)



death, a pathway that is often dysregulated in cancers but might be therapeutically targeted (Distelhorst and Bootman 2019; Ivanova et al. 2019).

Stimulation of cells with agonists that activate IP₃ production typically leads to the generation of cytosolic Ca²⁺ oscillations (sometimes referred to in the Ca²⁺ literature as “Ca²⁺ spikes” or “Ca²⁺ transients”) (Berridge and Galione 1988; Dupont et al. 2011). The patterns of Ca²⁺ oscillation can vary between cell types, and even within a cell type for different stimuli, but in most cases Ca²⁺ oscillations are brief increases in cytosolic Ca²⁺ that last for a few tens of seconds. Generally, Ca²⁺ oscillations have a rapid rising phase, reaching a peak cytosolic Ca²⁺ concentration ~500 nM, before more slowly decaying back to the resting basal Ca²⁺ concentration. It was demonstrated many years ago that intracellular signaling systems display oscillatory activity (Berridge and Rapp 1979), and that cellular Ca²⁺ signaling in particular was similarly encoded as oscillations (Woods et al. 1986). Studies have shown that both the frequency of Ca²⁺ oscillations displayed by cells (Rooney et al. 1989) and the downstream cellular responses (Dolmetsch et al. 1998) are proportional to the concentration of stimulus applied. Hence, Ca²⁺ signaling is often considered as information transmission in a frequency-encoded manner where the successive pulses of cytosolic Ca²⁺ that arise with each Ca²⁺ oscillation trigger a cumulative cellular response (Bhattacharyya et al. 2019; Roy and Cyert 2019).

Ca²⁺ OSCILLATIONS AS A HIGH-FIDELITY SIGNALING MECHANISM

There are a number of advantages to using oscillatory Ca²⁺ signals for information transfer within cells. As mentioned earlier, sustained increases in cytosolic Ca²⁺ are energetically costly as they need to overcome cellular Ca²⁺ transport processes, and if the Ca²⁺ elevation is too great it may cause deleterious effects. So, Ca²⁺ oscillations are energetically more favorable. Additionally, there is considered to be greater fidelity in frequency-encoded signaling systems than those based on graded amplitude changes (Berridge

1997). Moreover, cells have mechanisms for decoding, and responding to, pulsatile increases in Ca²⁺ in preference to sustained Ca²⁺ signals (Hajnóczky et al. 1995). An important mechanism by which Ca²⁺ signals are decoded involves phosphorylation-dependent control of proteins via both kinases and phosphatases that are activated by Ca²⁺, such as Ca²⁺/calmodulin-dependent kinase II and calcineurin (Bhattacharyya et al. 2019; Roy and Cyert 2019). Additionally, the Ca²⁺-binding protein calmodulin mediates a number of cytosolic and nuclear effects of Ca²⁺ signals (Hagenston et al. 2019). The mechanism through which cells generate Ca²⁺ oscillations is still not completely understood, particularly for situations where there is an interval of many tens of seconds, or even minutes, between successive cytosolic Ca²⁺ increases (Skupin et al. 2008). A common mechanism invoked to explain cytosolic Ca²⁺ oscillations is based on the feedback of Ca²⁺ itself on IP₃Rs. Indeed, IP₃R activation has a “bell-shaped” dependence on cytosolic Ca²⁺: relatively low Ca²⁺ concentrations (250–500 nM) promote Ca²⁺ release, whereas greater Ca²⁺ concentrations (~1 μM) inhibit Ca²⁺ release (Bezprozvanny et al. 1991; Prole and Taylor 2019).

Following stimulation of cells with an agonist that activates phospholipase C, IP₃ produced at the plasma membrane will diffuse within the cytosol and bind to its receptor, IP₃R, on intracellular organelles. At first, the Ca²⁺ signal is limited, but as the cytosolic Ca²⁺ concentration increases it can feed back in a positive manner to stimulate further Ca²⁺ release, a process known as Ca²⁺-induced Ca²⁺ release (Roderick et al. 2003). However, as the cytosolic Ca²⁺ concentration continues to increase it will reach the range in which the feedback becomes inhibitory. At that point the IP₃Rs will close and the cell can then recover back to the resting situation as Ca²⁺ is transported out the cell and back into the stores (Fig. 4). In this scheme, IP₃Rs require IP₃ binding to become activated, but are actually opened and closed by Ca²⁺ binding to discrete stimulatory and inhibitory sites, respectively. As discussed above, Ca²⁺ influx plays a part in restoring the Ca²⁺ content of the stores so that the cell is set for another oscillatory cycle. In fact,

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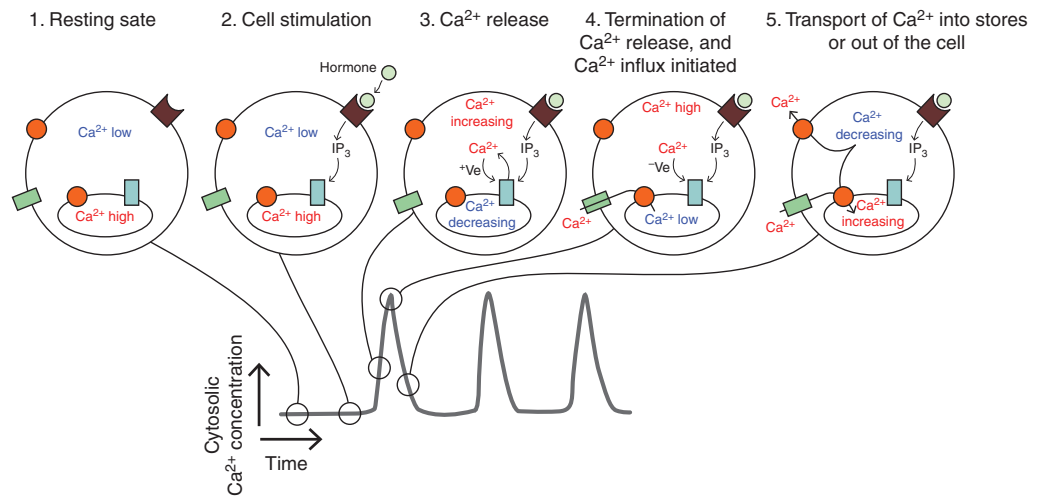


Figure 4. Generation of Ca^{2+} oscillations via positive and negative feedback on IP_3Rs . The sequence of cartoons 1–5 depict the status of cytosolic Ca^{2+} , IP_3R activity, and Ca^{2+} store content during the various phases of a Ca^{2+} oscillation. Phase 1 represents the cell at rest, before application of an extracellular stimulus. Phase 2 shows the cell subsequent to agonist–receptor interaction, when there is IP_3 production but no Ca^{2+} release via IP_3Rs . Phase 3 indicates the initial opening of IP_3Rs and an increasing cytosolic Ca^{2+} concentration, which exerts a positive (+Ve) feedback on the IP_3R , thereby promoting further Ca^{2+} release. At phase 4, the cytosolic Ca^{2+} concentration has increased to the point where it inhibits IP_3R activity via negative (–Ve) feedback and hence Ca^{2+} release terminates. At this point, the Ca^{2+} store is depleted and Ca^{2+} influx is activated. Phase 5 indicates the recovery of the cell as Ca^{2+} is transported from the cytosol toward the intracellular stores and the extracellular environment and the negative feedback from cytosolic Ca^{2+} is relaxed.

altering the concentration of extracellular Ca^{2+} has a significant effect on the frequency of cytosolic Ca^{2+} oscillations, suggesting that the loading of intracellular Ca^{2+} stores is a key aspect of a cell recovering from one Ca^{2+} release event to the next (Bootman et al. 1996).

Hormone-evoked Ca^{2+} oscillations originate in the cytosol through initial activation of clusters of IP_3Rs . Intriguingly, not all IP_3Rs are equal in this respect and only a fraction of the IP_3Rs that are expressed, specifically those within clusters, seem to be able to respond (Prole and Taylor 2019). The activation of clusters of IP_3Rs has been visualized using rapid imaging techniques, and the localized cytosolic Ca^{2+} elevation caused by the activation of an IP_3R cluster is termed a “ Ca^{2+} puff” (Yao et al. 1995; Bootman et al. 1997). With low levels of cell stimulation, and consequently low intracellular levels of IP_3 , a few Ca^{2+} puffs may be all that occurs. However, with higher levels of cell stimulation the Ca^{2+} that diffuses from one cluster of IP_3Rs during

a Ca^{2+} puff is likely to encounter a neighboring cluster in which the IP_3Rs are liganded with IP_3 . In that case, the second IP_3R cluster can be triggered and a further Ca^{2+} puff will occur. Through successive rounds of diffusion and Ca^{2+} -induced Ca^{2+} release, neighboring IP_3R clusters can be recruited and Ca^{2+} signals can propagate throughout a cell. Saltatoric Ca^{2+} waves, which reflect this fire–diffuse–fire scheme for Ca^{2+} signal propagation (Thul et al. 2008), have been visualized in the cytosol of a number of cell types including nonexcitable cells (Bootman et al. 1997; Callamaras et al. 1998), cardiac myocytes (Kockskämper et al. 2001), and also the nanotunnels that connect the cytoplasm of adjacent cells (Smith et al. 2011). As Ca^{2+} waves propagate through cells, they encounter effector proteins that can become activated (Schwaller 2019), as well as other organelles that may sequester, or respond to, the oncoming Ca^{2+} signal. Moreover, Ca^{2+} waves can permeate the nucleoplasm by diffusing through nuclear pore



complexes (Bootman et al. 2009), and thereby modulate gene transcription (Hagenston et al. 2019). As a result of the relative lack of Ca^{2+} sequestration within the nucleus, Ca^{2+} increases within this organelle can persist for longer than in the cytosol (Lipp et al. 1997), and indeed have discrete functions (Higazi et al. 2009; Hagenston and Bading 2011).

Although Ca^{2+} oscillations constitute a form of cell signaling that is used by many cell types for the reasons described above, there are numerous examples of cellular responses being controlled by the amplitude/kinetics (Dolmetsch et al. 1997), or spatial extent, of cytosolic Ca^{2+} signals (Mackenzie et al. 2004). Indeed, sometimes there is an interplay of different parameters in controlling cellular responses. Within the heart for example, β -adrenergic receptor stimulation causes higher amplitude Ca^{2+} signals that contribute to stronger contraction (positive inotropy), faster kinetics for Ca^{2+} signal recovery (positive lusitropy to enable the heart to relax quicker), and a faster rate of beating (positive chronotropy; although in the intact heart faster beating is caused by more frequent action potentials arising from the sinoatrial node pacemaker).

LOCAL Ca^{2+} SIGNALS AND MEMBRANE CONTACT SITES ENABLE DISCRETE COMMUNICATION

Earlier in this article, it was mentioned that averaged Ca^{2+} signals within cells are typically seen to reach peak levels of 0.5–1 μM . However, it is important to point out that at the mouth of an open Ca^{2+} channel (or Ca^{2+} channel cluster) the concentration of Ca^{2+} can reach in excess of 100 μM (Thul and Falcke 2004; Demuro and Parker 2006). The concentration of Ca^{2+} falls dramatically with distance from an active channel, because of dissipation via diffusion and buffering (Thul and Falcke 2004). So, when a cell is stimulated, Ca^{2+} increases of many tens of micromolar will develop around the locations of the activated Ca^{2+} channels, and diffusion of Ca^{2+} away from these channels will yield a more widespread distribution of Ca^{2+} with a substantially lower Ca^{2+} concentration. The

regions of high Ca^{2+} concentration around activated Ca^{2+} channels have been increasingly recognized as having distinct signaling functions (Barak and Parekh 2019; Wang et al. 2019) and are often referred to as “ Ca^{2+} signaling microdomains” (or nanodomains, depending on the distance involved; sometimes the terms “ Ca^{2+} hotspots” or “local Ca^{2+} signals” are used in the literature). Some Ca^{2+} -sensitive effectors are localized close to Ca^{2+} channels, thereby providing a means for rapid and specific cellular outcomes (Bootman et al. 2001; Berridge 2006).

Ca^{2+} signaling microdomains also occur because of the close apposition of cellular organelles (Ahuja et al. 2019), for example, between the ER and mitochondria, the ER and lysosomes, or organelles with the plasma membrane (La Rovere et al. 2016; Raffaello et al. 2016; Csordás et al. 2018). Ca^{2+} signaling microdomains are a rapidly growing aspect of the wider topic of membrane contact sites in cell biology (Dolgin 2019; Scorrano et al. 2019). The close proximity of organelles and membranes is brought about through tethering proteins (Scorrano et al. 2019), thereby enabling Ca^{2+} signals originating at one membrane to activate processes at the apposed membrane. These membrane contact sites limit the diffusion of Ca^{2+} and provide a means for highly specific interactions between Ca^{2+} sources and effectors. Examples of four different Ca^{2+} signaling mechanisms in which membrane contact sites are essential are depicted in Figure 5. Although the four examples shown in Figure 5 are all based on the essential apposition of cellular organelles/membranes, they are different in terms of Ca^{2+} toolkit components and physiological outcomes.

Store-operated Ca^{2+} entry (SOCE) (Fig. 5A) was postulated many years ago to explain the observation that depletion of intracellular Ca^{2+} stores led to Ca^{2+} influx across the plasma membrane (Putney 1990; Ahuja et al. 2019; Lewis 2019). Moreover, a highly Ca^{2+} -selective current was identified that was triggered by Ca^{2+} store depletion (Hoth and Penner 1992). This current was termed “ Ca^{2+} release-activated current” (I_{CRAC}) and it is the electrophysiological basis of SOCE. The molecular components of SOCE were established sometime later: stromal inter-

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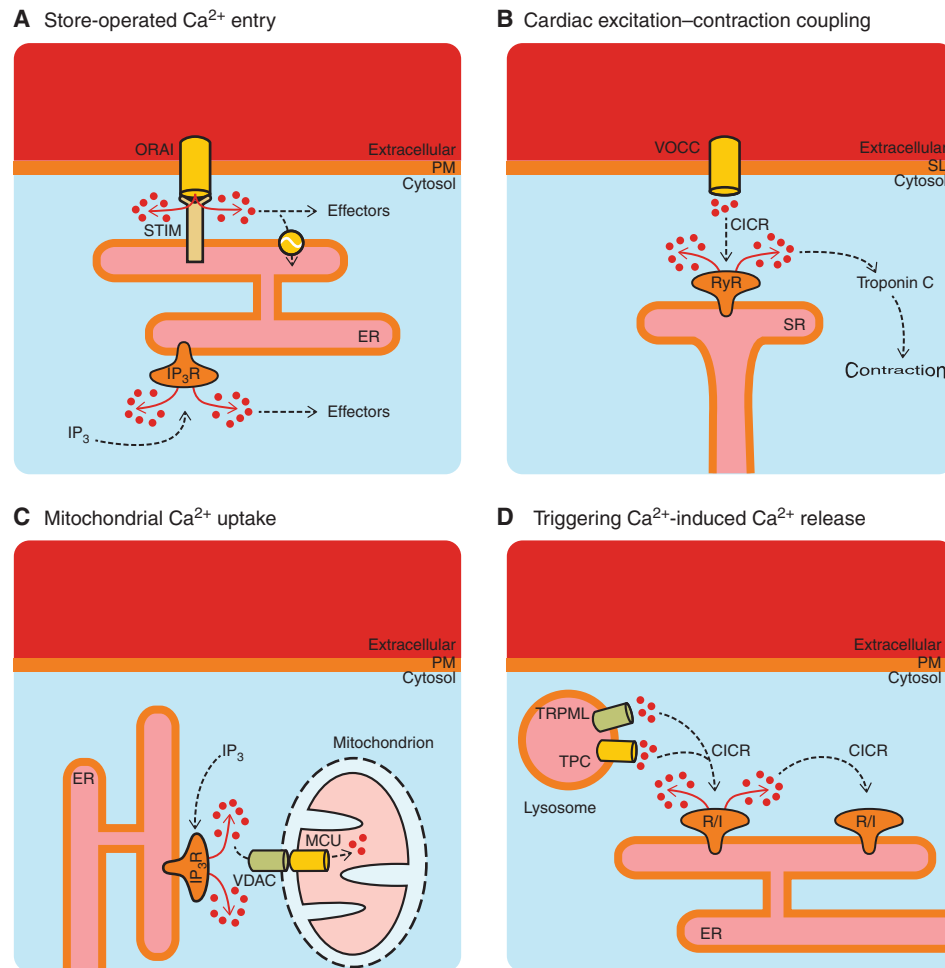


Figure 5. Examples of Ca²⁺ signaling via membrane contact sites. (A)–(D) Well-known situations where the close apposition of membranes/organelles is essential for initiation or communication of Ca²⁺ signals. VOCC, voltage-operated Ca²⁺ channel; SL, sarcolemma; VDAC, voltage-dependent anion channel; MCU, mitochondrial Ca²⁺ uniporter; TPC, two-pore channel; TRPML, mucolipin subfamily of transient receptor potential channels; CICR, Ca²⁺-induced Ca²⁺ release; R/I, ryanodine receptor or IP₃ receptor.

action molecule (STIM), which acts as a sensor of ER luminal Ca²⁺ loss (Liou et al. 2005; Zhang et al. 2005), and Orai, which forms the Ca²⁺ channel in the plasma membrane (Prakriya et al. 2006). STIM is a transmembrane protein that spans the ER and projects its carboxy terminus into the cytosol. A substantial amount of work has been focused on understanding how STIM regulates SOCE (Lewis 2019). Briefly, STIM can bind Ca²⁺ within the lumen of the ER, and if the Ca²⁺ concentration drops below

a threshold level then Ca²⁺ dissociates from STIM. Consequently, STIM oligomerizes and triggers the opening of Orai channels at the plasma membrane (Soboloff and Romanin 2019). The loss of Ca²⁺ from STIM causes substantial molecular rearrangements within the STIM protein such that its carboxy-terminal domain projects toward Orai channels so that they physically interact. This interaction occurs in regions where the ER and plasma membrane come within 15 nm of each other (Zhou et al. 2017).



In addition to Orai, SOCE can be mediated by members of the transient receptor potential (TRP) family, and in particular the subfamily of canonical TRP channels (TRPCs) (Ahuja et al. 2019; Ong and Ambudkar 2019; Vangeel and Voets 2019). Indeed, Orai and TRPC channels can cooperate in the activation of Ca^{2+} entry (Ambudkar et al. 2017). Ca^{2+} store depletion and STIM1–Orai interaction leads to the insertion of TRPCs into the plasma membrane. The participation of TRPCs alongside Orai prolongs SOCE and downstream signaling (Cheng et al. 2011). The interaction of STIM1, Orai, and TRPCs gives rise to a current that has been termed I_{SOC} , which is distinct from I_{CRAC} (Desai et al. 2015). Insights into the properties and mode of TRP activation have been propelled forward by advances in structural information (Vangeel and Voets 2019).

Excitation–contraction coupling in cardiac myocytes (Fig. 5B) also relies on the close apposition of the cell membrane with a major intracellular Ca^{2+} store, but in this case it is the sarcolemma (the myocyte cell membrane) and the SR (the Ca^{2+} store within muscle cells that is used to activate contraction). The Ca^{2+} channels responsible for myocyte contraction are voltage-operated Ca^{2+} channels (specifically, $\text{Ca}_v1.2$ or “L-type” voltage-operated Ca^{2+} channels) on the sarcolemma, and RyRs on the SR. RyRs are primarily activated by Ca^{2+} , but can also respond to cellular messengers such as cyclic adenosine diphosphate ribose (Galione and Churchill 2000).

Blood pumping by the heart occurs via the coordinated contraction of the atrial and ventricular chambers in a process known as the cardiac cycle (Bers 2002). Each cardiac cycle is initiated by a group of specialized pacemaking cells in the right atrial chamber (the sinoatrial node), which spontaneously discharge electrical signals (action potentials) that propagate through the heart. Ca^{2+} is the cellular messenger that links propagating action potentials and cardiomyocyte contraction (Gilbert et al. 2019). When an action potential arrives at a cardiac myocyte, it triggers a brief depolarization of the sarcolemma, which consequently activates the voltage-operated Ca^{2+} channels, leading to the

influx of Ca^{2+} from outside of the cells into a membrane-delimited region called the dyadic cleft (Eisner et al. 2017). The sarcolemma and SR come within 10–15 nm of each other at a dyadic cleft. This proximity is necessary so that the Ca^{2+} influx through voltage-operated Ca^{2+} channels can diffuse to the RyRs present on the SR membrane at a concentration sufficient to trigger Ca^{2+} -induced Ca^{2+} release (Fearnley et al. 2011).

The activation of RyRs leads to a rapid increase of the Ca^{2+} concentration within the dyadic cleft. The Ca^{2+} signal within the dyadic cleft subsequently diffuses out into the cytoplasm and encounters troponin C (among other targets), which promotes the association of actin and myosin to trigger cell contraction. A single cardiac myocyte contains thousands of dyadic clefts that simultaneously respond during an action potential, and all contribute to the Ca^{2+} signal that is required for contraction. It has been suggested that around 25 voltage-operated Ca^{2+} channels and 100 RyRs are closely apposed within a single dyadic cleft (Bers and Guo 2005). In some cardiac diseases, the sarcolemma and SR membranes become dissociated such that there is no cross talk between voltage-operated Ca^{2+} channels and RyRs (Louch et al. 2004). These “orphaned RyRs” are not recruited during excitation–contraction coupling, hence myocyte Ca^{2+} signaling and contraction become weaker (Heinzel et al. 2011).

Mitochondrial Ca^{2+} uptake (Fig. 5C) relies on the close association of mitochondria to Ca^{2+} channels. In fact, mitochondria can accumulate Ca^{2+} from various sources (i.e., Ca^{2+} release from organelles and Ca^{2+} influx) (Collins et al. 2001). However, the rate of Ca^{2+} uptake by mitochondria depends on the proximity of these organelles to Ca^{2+} channels. It was demonstrated some time ago that mitochondria are relatively insensitive to the average measured cytosolic Ca^{2+} concentrations that occur during cell stimulation (i.e., 100–500 nM) (Kirichok et al. 2004), and that mitochondrial Ca^{2+} uptake relies on the microdomains of high Ca^{2+} concentration that occur close to activated channels (Rizzuto et al. 1993; Csordás et al. 1999). Mitochondria-associated membranes (MAMs) are a specific form

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of membrane contact site, and are intensely studied as sites of Ca^{2+} communication between the ER and mitochondria (in addition to being sites of protein and lipid transfer) (Marchi et al. 2018). This interorganellar complex enables the “quasisynaptic” transfer of Ca^{2+} between the ER and mitochondria (Rizzuto et al. 1998; Csordás et al. 1999).

Within MAMs, IP_3Rs on the ER membrane are coupled via chaperones with voltage-dependent anion channels (VDACs) situated in the outer mitochondrial membrane (Szabadkai et al. 2006). VDAC proteins permit the passage of Ca^{2+} across the outer mitochondrial membrane. Ca^{2+} transport across the inner mitochondrial membrane is enabled by the mitochondrial Ca^{2+} uniporter complex (Granatiero et al. 2017), which has key roles in cell death (Penna et al. 2018), organ physiology (Mammucari et al. 2018), and disease (Mammucari et al. 2017). Changes in MAM organization have been linked to neurodegenerative diseases and cancer (Kerkhofs et al. 2017; Rossi et al. 2019). Moreover, the cellular sensitivity of cancer cells toward chemotherapeutics seems to be dependent on Ca^{2+} fluxes at the MAMs (Kerkhofs et al. 2018). These insights offer novel opportunities to promote cancer cell death, for example through novel peptide tools that act at the MAM interface (Kerkhofs et al. 2019).

Triggering of Ca^{2+} -induced Ca^{2+} release (Fig. 5D) can occur when Ca^{2+} channels are in close proximity. As mentioned above, IP_3Rs and RyRs are activated by an increase in the cytosolic Ca^{2+} concentration (Bezprozvanny et al. 1991). Both types of channel have been shown to amplify small Ca^{2+} signals into much larger responses via Ca^{2+} -induced Ca^{2+} release. This amplification is critical for relatively small Ca^{2+} stores such as lysosomes to trigger substantial cellular Ca^{2+} signals (Galione 2019). For example, the cellular messenger nicotinamide adenine dinucleotide phosphate can cause a limited release of Ca^{2+} from lysosomes via TPCs (Lloyd-Evans and Waller-Evans 2019), which can then be amplified by IP_3Rs and RyRs (Zhu et al. 2010). IP_3Rs have been found to be strategically located within ER-lysosomal contact sites (Atakpa et al. 2018), where they serve to deliver

Ca^{2+} from the ER to the lysosomal compartment (Patel 2019).

CONCLUDING REMARKS

Cellular Ca^{2+} signaling is complex, multifactorial, and dynamic, and is critical to many physiological processes. Ca^{2+} signals can arise from a number of sources and via a plethora of channels and other transporters. Ca^{2+} signaling is tightly integrated with other cellular signal transduction pathways, and there are many examples of cross talk and synergy. Cellular signaling can remodel depending on environmental conditions, and alterations to Ca^{2+} signals or Ca^{2+} homeostasis occur in disease conditions. The discussion above is a necessarily superficial tour of some of the key aspects of cellular Ca^{2+} signaling. For each of the topics discussed, there is a wealth of underlying publications and knowledge. The intention of this article was to stimulate appreciation of Ca^{2+} signaling so that the interested enquirer might continue reading. Fortunately, while the Ca^{2+} signaling literature is vast, there are some underpinning principles of Ca^{2+} signaling that apply irrespective of the cell type and its function. In particular, Ca^{2+} signals are highly organized in terms of kinetics and cellular location. The organization of Ca^{2+} signals enables cells to use Ca^{2+} as a means of simultaneously controlling diverse processes. It is clear that perturbations of Ca^{2+} signaling are a proximal factor in the pathogenesis of debilitating and fatal pathologies, but our increasing understanding of aberrant Ca^{2+} signals offers unprecedented opportunities for novel therapeutic strategies.

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