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Biochemistry of calcium oscillations

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ABSTRACT

Cytosolic calcium (Ca^{2+}) oscillations are vastly flexible cell signals that convey information regulating numerous cellular processes. The frequency and amplitude of the oscillating signal can be varied infinitely by concerted actions of Ca^{2+} transporters and Ca^{2+}-binding proteins to encode specific messages that trigger downstream molecular events. High frequency cytosolic Ca^{2+} oscillations regulate fast responses, such as synaptic transmission and secretion, whereas low frequency oscillations regulate slow processes, such as fertilization and gene transcription. Thus, the cell exploits Ca^{2+} oscillations as a signalling carrier to transduce vital information that controls its behaviour. Here, we review the underlying biochemical mechanisms responsible for generating and discriminating cytosolic Ca^{2+} oscillations.

1. The history of Ca^{2+} oscillations

The first piece in the calcium (Ca^{2+}) signalling jigsaw puzzle was laid by Sydney Ringer more than a century ago, in 1883, when he discovered that hearts contracted in London tap water but failed to do so in distilled water [1,2]. Since then thousands of publications have reported Ca^{2+} signals in various cell types. Cytosolic Ca^{2+} signals appear in many shapes and can simply be classified as transient, sustained or oscillatory signals. Proteins within the cell have the capacity to decipher information in these multifaceted Ca^{2+} signals and subsequently activate different cellular programs. The oscillatory Ca^{2+} signals make a class of its own, since the frequency and amplitude can be varied infinitely. Identifying the first report describing cell signalling via Ca^{2+} oscillations is difficult because the role of Ca^{2+} oscillations as information carrier was not known at that time. Maybe the first article presenting cytosolic Ca^{2+} oscillations as a signalling mechanism was published by Endo et al. in 1970 and demonstrated ryanodine receptor (RyR) regulated Ca^{2+} oscillations in skeletal muscle fibres [3]. A few years later in 1976 another central paper by Kuba et al. speculated that membrane potential oscillations in neurons were driven by Ca^{2+} [4]. Later this and other important studies [5] on Ca^{2+}-dependent membrane potential fluctuations were concluded to be the effect of cytosolic Ca^{2+} oscillations. One of the earliest studies to directly show cytosolic Ca^{2+} oscillations in single cells, using the Ca^{2+} sensitive fluorescent protein aequorin, was published by Ridgway et al. in 1976 [6].

The field of Ca^{2+} oscillations entered a new era after 1983 when inositol-1,4,5-trisphosphate ($InsP_3$) was discovered to release Ca^{2+} from nonmitochondrial intracellular stores [7]. Among all of the prominent researchers that have contributed to the general understanding of Ca^{2+} signalling, Michael Berridge is probably the one that stands out the most with his groundbreaking discoveries on $InsP_3$-mediated Ca^{2+}-release and his many excellent reviews [7–9]. However, despite more than 120 years of active research in the field of Ca^{2+} signalling there are still many missing pieces in the jigsaw puzzle.

2. Generation of cytosolic Ca^{2+} oscillations

The Ca^{2+}-ion is the most widespread cation in the human body and it is uniquely suited for signal transduction [9,10]. With a low cytosolic resting concentration, $\sim 10^{-7}$ M, and a high extracellular concentration, $\sim 10^{-3}$ M, Ca^{2+} fluctuations can be generated and detected with only a relatively small increment of Ca^{2+} added to the cytoplasm. Increase in the cytosolic Ca^{2+} concentration is driven by the aforementioned large gradient, $\sim 10^4$, and occurs via influx through integral plasma membrane channel proteins or through release from channels located on intracellular compartments (discussed below). High sustained levels of Ca^{2+} in the cytoplasm are toxic to the cell and can result in cell death through both necrosis and apoptosis [11]. Cells have therefore developed transporters that quickly clear Ca^{2+} increases from the cytoplasm (discussed below).

The low basal cytosolic Ca^{2+} concentration is kept in equilibrium through a delicate balance between influx and efflux of Ca^{2+}. However, the equilibrium can be perturbed in many ways (discussed below) causing more Ca^{2+}-ions to enter the cytoplasm than are cleared. Clearing mechanisms in the cell then try to rapidly restore the low resting concentration of cytosolic Ca^{2+}. If successful, a Ca^{2+} transient is generated, and if not, the high

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concentration of Ca^{2+} will drive the cell into apoptosis or necrosis. Under certain conditions, when the Ca^{2+} regulatory system is disturbed, the cell can only partly restore the low Ca^{2+} level. The cell's inability to regulate and maintain a low steady state concentration of Ca^{2+} will result in trains of periodic Ca^{2+} transients. This Ca^{2+} oscillatory signal is generated by concerted actions of distinct cellular Ca^{2+} transporters and can have large spatial and temporal variations depending on the type of stimuli and cellular context. If the intracellular Ca^{2+} concentration remains disturbed, different transcription programs are activated that fine-tune the Ca^{2+} regulatory machinery to regain control of the cytosolic Ca^{2+} level.

Despite the many reports on Ca^{2+} oscillations, a unifying mechanism generating the oscillatory response has not been fully elucidated. It is also not clear how the frequency of the oscillatory signal is set. However, there are demonstrations of cell mechanisms altering the Ca^{2+} oscillation frequency [12–15]. Crosstalk between parallel cellular signalling pathways, for example cyclic AMP signalling, can affect the frequency of Ca^{2+} oscillations [14,16].

3. Ca^{2+}-increase mechanisms

The oscillatory signal is initiated when the equilibrium in the basal cytosolic Ca^{2+} level is perturbed somehow. This can occur when the cell senses extracellular stimuli that result in activation of channels that transport Ca^{2+} into the cytoplasm (Fig. 1). Such channels are located either in the plasma membrane or in the membrane of the endoplasmic/sarcoplasmic reticulum (ER/SR). The nature of the perturbating stimuli is diverse, including membrane voltage alterations, cell-to-cell interactions, and extracellular substances that bind specific receptors.

Channels in the plasma membrane that transport Ca^{2+} into the cytoplasm are voltage-dependent Ca^{2+} channels and receptor regulated ionotropic Ca^{2+} channels (Fig. 1). Changes in membrane potential activates Ca^{2+} influx through voltage-dependent Ca^{2+} channels, that perturb the basal Ca^{2+} equilibrium which can result in cytosolic Ca^{2+} oscillations [17]. Glutamate, the major excitatory neurotransmitter in the brain, acts on the ionotropic Ca^{2+} channels alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA). Both AMPA and NMDA receptor activation have been reported to induce Ca^{2+} oscillations [18]. Adenosine Triphosphate (ATP), which activates the purinergic P2X ionotropic Ca^{2+} channels and metabotropic P2Y receptors (P2YR), is also known to trigger Ca^{2+} oscillations [19]. Other well known plasma membrane metabotropic receptors that trigger cytosolic Ca^{2+} oscillations include the muscarinic Acetylcholine receptors (mAChR) [20] and the metabotropic Glutamate receptor 5 (mGluR5) [21]. In addition, activation of receptor tyrosine kinases (RTKs) is likewise known to trigger cytosolic Ca^{2+} oscillations [15].

Cytosolic Ca^{2+} can also increase upon release of Ca^{2+} from intracellular ER/SR Ca^{2+} stores. The release occurs mainly through $InsP_3$ receptors ($InsP_3Rs$) and RyRs (Fig. 1).

The ubiquitous $InsP_3R$ is a Ca^{2+}-release channel on intracellular ER Ca^{2+} stores that plays an important role in cytosolic Ca^{2+} signalling [22], in both excitable and non-excitable cells. The $InsP_3R$ gene encodes a ~2700 amino-acids (1000 kDa) protein with ~5% composing the ion conduction pore and ~95% potential recognition sites for interacting proteins [23]. Binding of a ligand to metabotropic receptors, such as P2YR, mAChR, and mGluR5, or RTKs leads to the activation of phospholipase C (PLC) which catalyses the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) to produce $InsP_3$ and diacylglycerol. When $InsP_3$ binds to the $InsP_3R$ it causes

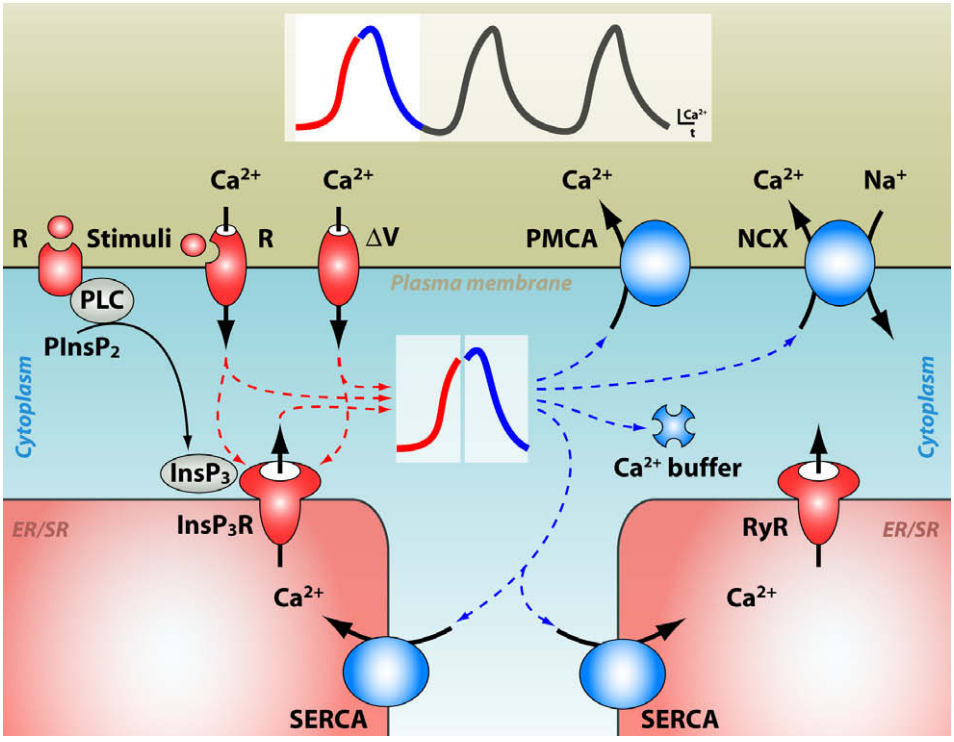

Fig. 1. Cartoon illustrating the main mechanisms involved in the generation of cytosolic Ca^{2+} oscillations. Cytosolic Ca^{2+} oscillations are generated through the concerted action of cellular mechanisms that increase (red) and decrease (blue) the concentration of Ca^{2+} in the cytoplasm. Oscillatory signals are initiated by stimuli that trigger entry of external Ca^{2+} through receptor (R) or voltage (ΔV) gated Ca^{2+} channels in the plasma membrane or by activation of receptors (R) that stimulate PLC and $InsP_3$-mediated Ca^{2+}-release from the ER/SR. When the cytosolic level of Ca^{2+} increases, Ca^{2+} itself stimulates $InsP_3Rs$ and/or RyRs to release further Ca^{2+} into the cytoplasm. During this phase, Ca^{2+} buffers bind Ca^{2+} which contributes to the decrease in the cytosolic concentration of free Ca^{2+}. When the Ca^{2+} concentration reaches high levels, the plasma membrane Ca^{2+}-ATPase (PMCA) and Na^+/Ca^{2+}-exchanger (NCX) extrude Ca^{2+} to the outside, whereas the ER/SR Ca^{2+}-ATPase (SERCA) pumps Ca^{2+} back into the ER/SR.

a conformational change that opens an integral Ca^{2+} channel, allowing Ca^{2+} to flow out in the cytoplasm. Three subtypes (type 1–3) with cell specific expression patterns and different affinities for $InsP_3$, Ca^{2+}, and nucleotides have been discovered [22,24]. Both $InsP_3$ and Ca^{2+} are required to open $InsP_3$Rs. Depending on the cellular context, the $InsP_3$R can respond to Ca^{2+} in a bell-shaped fashion [25–27], a crucial property for the activation of a regenerative signal. The $InsP_3$R can also be phosphorylated by multiple kinases [24], modulating its properties and further fine-tuning oscillatory signals.

The RyR is a critical intracellular Ca^{2+}-release channel in all excitable cells [28]. In muscle cells it drives the essential process of excitation–contraction coupling. The RyR protein is composed of ~5000 amino-acids (560–600 kDa) and contains mainly two domains: a large (80%) N-terminal regulatory domain and a small C-terminal channel domain. Cloning of the RyR gene indicated that three subtypes (RyR1–3) coexist with tissue-specific expression patterns. The main activator of RyR is Ca^{2+} itself, with a K_d in the high 10^{-9} M range, although dependent on the subtype. As for the $InsP_3$R, excess Ca^{2+} has an inhibitory effect on the RyR (see below), depending on the subtype and cell type. Cyclic ADP ribose, a common second messenger, activates RyRs, whereas binding of, for example, caffeine, FK506 and ryanodine modulates Ca^{2+}-release via diverse molecular mechanisms [9,28].

A mechanism generally accepted to play a key role in generating Ca^{2+} oscillations is the positive feedback of Ca^{2+} itself in a process called Ca^{2+}-induced Ca^{2+}-release (CICR) [3,9,10]. This feedback mechanism amplifies the signal and acts on both $InsP_3$R and RyR. However, when the cytosolic level of Ca^{2+} increases above 10^{-6}–10^{-5} M, binding of Ca^{2+}-ions to inhibitory sites inhibits further release from $InsP_3$R and RyR (negative feedback).

When internal Ca^{2+} stores are depleted, a mechanism called store-operated Ca^{2+} (SOC) entry is activated, which causes Ca^{2+} to enter the cytoplasm, and ultimately ER/SR via Ca^{2+}-ATPases (SERCA), through plasma membrane channels (reviewed in [29]). This SOC entry is mainly found in non-excitable cells and is regulated by the STIM1 and Orai1 proteins. STIM1, located in the ER membrane, senses the ER depletion and activates the SOC channel Orai1, located in the plasma membrane.

4. Ca^{2+}-decrease mechanisms

As mentioned earlier, a sustained high cytosolic Ca^{2+} concentration is toxic to the cell. Therefore, the cell has developed mechanisms to clear high levels of cytosolic Ca^{2+} (Fig. 1). Excess of Ca^{2+} is mainly pumped into ER/SR stores via the SERCA or removed from the cell across the plasma membrane by Ca^{2+}-ATPases (PMCAs). The Na^+/Ca^{2+}-exchanger (NCX) can also transport Ca^{2+} out of the cell, depending on the ionic gradients across the membrane. Supporting these mechanisms, the mitochondrial uniporter acts to rapidly clear excess of cytosolic Ca^{2+} loads before slowly releasing Ca^{2+} back to the cytoplasm where it is dealt with by the aforementioned pumps. These pumping mechanisms are activated at different concentrations of cytosolic Ca^{2+} and have different transport rates. The SERCA and PMCA have high affinities and low transport rates while the mitochondrial uniporter and NCX have lower affinity and high transport rates [9]. Thus, cells are able to express various combinations of these Ca^{2+} pumps that suit their specific Ca^{2+} signalling needs. For example, cells that are producing fast Ca^{2+} oscillations, such as cardiomyocytes, have PMCA isoforms (PMCA2a and PMCA3f) with high transport rates, whereas cells that produce slower Ca^{2+} oscillations to activate proliferation express pumps (PMCA4b) that pump with low transport rates [30].

As mentioned previously, the CICR feedback mechanism has also a negative variant as Ca^{2+} inhibits further release from RyR and $InsP_3$R, at high cytosolic concentrations of Ca^{2+} [9,10]. Among the three subtypes of $InsP_3$Rs, different characteristics in response to Ca^{2+} have been reported, where only the type 1 $InsP_3$R is exclusively inhibited by high concentrations of Ca^{2+}. High levels of Ca^{2+} do not inhibit the type 3 $InsP_3$R when activity is measured in planar lipid bilayers [31], whereas the type 2 $InsP_3$R is inhibited by high Ca^{2+} in an intact cellular context [26]. A similar situation can be found amongst the RyR subtypes, where RyR1 seems to be the most sensitive to negative Ca^{2+} feedback [9,28].

There are several proteins within the cell that temporally and spatially fine-tune the cytosolic Ca^{2+} oscillatory signal. The human genome encodes ~200 different Ca^{2+}-binding proteins [10]. These proteins, such as parvalbumin, calbindin, and calretinin, have different buffering capacities as well as cellular expression patterns and contribute to decreasing the cytosolic concentration of free Ca^{2+} [9]. The Ca^{2+}-binding sites of these proteins start to become occupied already during the rising phase of the Ca^{2+} transient when Ca^{2+}-ions enter the cytoplasm. Unloading of the proteins occur during the recovery phase. Gap junctions in the plasma membrane can also participate to decrease high levels of Ca^{2+} in the cytoplasm and thereby modulate the oscillatory signal by transporting excess of Ca^{2+} and/or small molecules such as $InsP_3$ to neighbouring cells [32].

5. Decoding Ca^{2+} oscillations

When a Ca^{2+} signal propagates through the cytoplasm of the cell, several Ca^{2+} sensors can translate the signal into cellular responses. Amplitude and frequency modulation are then exploited to encode the signal to carry information [33]. A number of proteins have been proposed as decoders of Ca^{2+} oscillations of which calmodulin (CaM) has been most extensively studied [34]. CaM is a ubiquitously expressed dumbbell-shaped 17 kDa protein with each globular end containing two EF-hands connected by a flexible α-helix [34]. Virtually all Ca^{2+}-binding proteins have the same EF-hand Ca^{2+}-binding domain, which consists of a twelve residue loop flanked on both sides by a twelve residue α-helix. Ca^{2+} binds CaM with a K_d around 10^{-6} M, making it an ideal Ca^{2+} sensor. Upon binding Ca^{2+}, CaM undergoes a conformational change, exposing hydrophobic residues that facilitate interactions of the Ca^{2+}/CaM complex with numerous target proteins, thereby potentially regulating their functionalities [35]. Ca^{2+}/CaM targets include several ion channels (in particular $InsP_3$R and RyR), pumps, transcription factors, and various rate-limiting enzymes. Among the target signalling proteins regulated by Ca^{2+}/CaM is a family of Ser/Thr protein kinases known as CaM-kinases (CaMKs), of which CaMKII has been proposed as a decoder of Ca^{2+} oscillations [36]. The biochemistry behind the decoding mechanism is not yet fully understood. However, autophosphorylation of CaMKII will take place if the magnitude or duration of the Ca^{2+} increase is right. The autophosphorylation occurs if two molecules of Ca^{2+}/CaM bind to two subunits on the same enzyme, one binds to a given subunit and activates it, while the second one binds to a neighbouring subunit, causing a conformational change that makes Thr286 available to its neighbour for phosphorylation. When CaMKII is phosphorylated it will remain active for several minutes even after the cytosolic Ca^{2+} concentration has returned to its basal level. If the next Ca^{2+} increase in the oscillatory signal is activated before all CaMKII are dephosphorylated, a frequency dependent accumulative effect is achieved. Thus, CaMKII can integrate the Ca^{2+} transients over time in an oscillatory signal, provided that they fall within the time window for dephosphorylation of the kinase. These properties give CaMKII the capacity to decode frequencies in Ca^{2+} oscillations.

6. Biological processes regulated by Ca^{2+} oscillations

There are numerous reports of biological events activated by cytosolic Ca^{2+} oscillations. In Table 1 we have listed a few recent

Table 1
Various biological processes regulated by cytosolic Ca^{2+} oscillations.

Biological process	Cell type	Inducer	Period	Ref(s)
Insulin secretion	Pancreatic β-cells	Glucose	10–210 s	[12,41]
Cell growth	Cardiac progenitors	Spontaneous[a]	~3 min	[13]
Gene expression (NFAT)	Cardiomyocytes	Spontaneous[a]	5–35 s	[15]
Interleukin production	Macrophages	ATP	~12 min	[19]
Fertilization	Mouse eggs	Sperm, ATP	10–40 min	[39]
Gene expression (c-fos)	Mast cells	Leukotriene C_4	~1 min	[42]
Gene expression (VCAM1)	Vascular endothelial cells	Artificial[b]	1–10 min	[43]
Hypertrophy	Cardiomyocytes	Spontaneous[a]	2–4 s	[44]
Glomerular filtration	Mesangial cells	Angiotensin II	~9 s	[45]
Pulmonary hypertension	Smooth muscle cells	5-HT/KCl	6–20 s	[46]
Neurite outgrowth	Neuroblastoma cells	Testosterone	~50 s	[47]
Dendritic growth	Cortical neurons	Ouabain	~20 s	[48]
Gene expression (Ras, ERK)	HeLa cells	Artificial[b]	~2 min	[49]
Substrate rigidity	Mesenchymal stem cells	Spontaneous[a]	~2 min	[50]

[a] Spontaneous Ca^{2+} oscillations are self-induced without any applied drug.
[b] Artificially induced Ca^{2+} oscillations.

examples of biological processes in different cell types that are regulated by cytosolic Ca^{2+} oscillations. One of the most extensively studied and spectacular event controlled by Ca^{2+} oscillations is the fertilization of the egg (reviewed in [37,38]). This discovery can be traced back almost one hundred years when egg activation was observed following injection of Ca^{2+} into the egg through a needle [10,37]. When the sperm interacts with the egg it triggers Ca^{2+} oscillations that continue for several hours [39]. The sperm injects PLC_ζ into the egg to stimulate the production of $InsP_3$ that activates the $InsP_3R$ [40]. The resulting Ca^{2+} oscillation triggers the developmental programme by activating the enzymatic machinery involved in cell division. Thereafter a spontaneous Ca^{2+} transient triggers cleavage of the one-cell embryo to form two daughter cells.

7. Conclusion

Cytosolic Ca^{2+} oscillations represent a highly diverse signalling system that regulates numerous processes in all cell types. Work to date has identified many proteins and mechanisms that trigger and modulate this universal signalling pathway. However, much of the molecular basis of the initiation, regulation and discrimination of Ca^{2+} oscillations remains to be addressed. The rapid development in live cell imaging and bio-probes will surely further our understanding of the nature and biochemistry of Ca^{2+} oscillations.

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