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ORIGINAL PAPER

Inositol 1,4,5-Trisphosphate Receptor Subtype-Specific Regulation of Calcium Oscillations

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Abstract Oscillatory fluctuations in the cytosolic concentration of free calcium ions (Ca^{2+}) are considered a ubiquitous mechanism for controlling multiple cellular processes. Inositol 1,4,5-trisphosphate (IP_3) receptors (IP_3R) are intracellular Ca^{2+} release channels that mediate Ca^{2+} release from endoplasmic reticulum (ER) Ca^{2+} stores. The three IP_3R subtypes described so far exhibit differential structural, biophysical, and biochemical properties. Subtype specific regulation of IP_3R by the endogenous modulators IP_3, Ca^{2+}, protein kinases and associated proteins have been thoroughly examined. In this article we will review the contribution of each IP_3R subtype in shaping cytosolic Ca^{2+} oscillations.

Keywords Inositol 1,4,5-trisphosphate receptor · Inositol 1,4,5-trisphosphate receptor-associated protein · Calcium signaling · Calcium oscillations

Abbreviations

Ca^{2+}	Calcium
CCK-OP	Cholecystokinin octapeptide
IP_3	Inositol 1,4,5-trisphosphate
IP_3R	IP_3 receptor
IP_3R1, 2 and 3	IP_3R subtype 1, 2, and 3
ER	Endoplasmic reticulum
PLC	Phospholipase C
IICR	IP_3-induced Ca^{2+} release
CaM	Calmodulin
PKA	cAMP-dependent protein kinase
PKC	Protein kinase C
CaMKII	Ca^{2+}/CaM-dependent protein kinase II
CTT	COOH-terminal tail
CICR	Ca^{2+}-induced Ca^{2+} release
AKAP	PKA-anchoring adaptor protein
LIZ	leucine/isoleucine zipper
PS	Presenilin
PS1 and PS2	Presenilin-1 and Presenilin-2
FAD	Familial Alzheimer's disease
GIT	G-protein-coupled receptor kinase-interacting protein
NCS-1	Neuronal Ca^{2+} sensor 1

Special Issue: In Honor of Dr. Mikoshiba.

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Introduction

Intracellular calcium (Ca^{2+}) dynamics play pivotal roles in numerous physiological processes, including fertilization, cell proliferation and differentiation, apoptosis, embryonic development, secretion, muscle contraction, immunity, brain function, chemical senses, and light transduction [1, 2]. Two main Ca^{2+} mobilizing systems co-exist in the cell: Ca^{2+} influx from the extracellular medium and Ca^{2+} release from internal stores. The inositol 1,4,5-trisphosphate (IP_3) receptor (IP_3R) is a tetrameric intracellular IP_3-gated Ca^{2+} release channel that is predominantly located on the membrane of the endoplasmic reticulum (ER). It is present in almost all cell types and plays a crucial role in converting extracellular stimuli into intracellular signals [1, 3]. Upon extracellular stimulation by various agonists, such as hormones, growth factors, neurotransmitters, neurotrophins, odorants, and light, Phospholipase-C (PLC) is activated and phosphatidylinositol 4,5-bisphosphate is

hydrolysated, generating IP_3. IP_3 binds to the IP_3R, leading to the IP_3-induced Ca^{2+} release (IICR) from the ER. Thirty years ago, Mikoshiba et al. found a mutant mouse with deficient Purkinje cells that had very low expression of P_{400}, a glycoprotein that was later uncovered as one of the IP_3R subtypes (IP_3R1) [4, 5]. In 1989, Mikoshiba and co-workers were the first group to reveal that IP_3R is a transmembrane protein and determine the primary sequence of IP_3R1, at the time the second largest molecule successfully cloned [6]. So far, three IP_3R subtypes (IP_3R1, IP_3R2, IP_3R3) as well as alternative splicing variants of IP_3R1 and IP_3R2 have been identified and cloned in mammals [1]. The expression patterns of the three subtypes are distinct but overlapping, and most cells express more than one subtype [7–9]. The three IP_3R subtypes share 65–85% homology and can be separated into five functional domains [1, 10–12]. The NH_2-terminal region contains a ligand coupling/suppressor domain, which suppresses IP_3-binding activity and determines different IP_3-binding affinity for each subtype [13], and an IP_3-binding core domain that is the minimum region required for specific IP_3 binding [14]. The ligand coupling/suppressor domain and the IP_3-binding core are often referred to as the IP_3-binding domain. Besides the IP_3-binding domain is the internal coupling domain, which confers regulation by various intracellular modulators (Ca^{2+}, calmodulin (CaM), ATP) and phosphorylation by several protein kinases (cAMP-dependent protein kinase (PKA), protein kinase C (PKC), cGMP-dependent protein kinase, Ca^{2+}/CaM-dependent protein kinase II (CamKII), and tyrosine kinase) [3]. The COOH-terminal region has a six membrane-spanning channel domain and a short cytoplasmic COOH-terminal tail (CTT), called the "gatekeeper domain", which is critical for IP_3R channel opening [10]. The Ca^{2+} release activity of the IP_3R channel is therefore regulated by many intracellular modulators (IP_3, Ca^{2+}, ATP, CaM), protein kinases, and IP_3R-binding proteins [1, 3], leading to various spatiotemporal cytosolic Ca^{2+} patterns and diverse cellular responses [1, 2]. The relatively low homology in the three IP_3R subtypes may underlie subtype-specific properties, that will affect Ca^{2+} signaling and in particular the spatiotemporal features of Ca^{2+} responses.

A prolonged elevation in the cytosolic Ca^{2+} concentration is considered toxic to the cell and in some cases may result in cell death. However, the cell can protect itself by temporally limiting the cytosolic Ca^{2+} elevation, often resulting in one of the most delicate patterns of Ca^{2+} signals, that being the oscillatory change in the cytosolic Ca^{2+} concentration, or Ca^{2+} oscillations [15–17]. Extensive studies over the past 30 years have revealed that cytosolic Ca^{2+} oscillations are ubiquitous and diverse cellular signals that control multiple processes in the cell. With cytosolic Ca^{2+} oscillations, cells not only avoid deleterious effects of sustained cytosolic Ca^{2+} concentrations, but also send out information encoded in the frequency and/or the amplitude of the oscillations to modulate cellular activity [15]. This review focuses on the separate role of the IP_3R subtypes in generating Ca^{2+} oscillations and on the molecular mechanisms responsible for the specific role of each subtype in regulating this ubiquitous signal.

A General Mechanism Generating Ca^{2+} Oscillations Based on Regulation of IP_3R

Many studies have indicated that IP_3R is involved in generating cytosolic Ca^{2+} oscillations [15–17]. For instance, the FGF-induced Ca^{2+} oscillations in mice fibroblasts are inhibited by an IP_3R antagonist [18]. Ca^{2+} oscillations are thought to arise due to periodic release of Ca^{2+} from intracellular Ca^{2+} stores via IP_3R [19]. Early studies using reconstituted IP_3R in lipid bilayers have indicated that Ca^{2+} can both activate and inhibit IP_3R [20, 21]. The IP_3R is activated at low cytosolic Ca^{2+} concentrations, elevating the cytosolic Ca^{2+} concentration through a process often referred to as Ca^{2+}-induced Ca^{2+} release (CICR). High cytosolic Ca^{2+} concentration can instead inhibit IP_3R, leading to a decrease in intracellular Ca^{2+} release. In vivo, the binding of IP_3 together with fluctuating cytosolic Ca^{2+} concentrations can trigger successive cycles of IP_3R activation and inhibition, which result in cytosolic Ca^{2+} oscillations. Accordingly, Ca^{2+} oscillations can be produced by application of IP_3 to permeabilized hepatocytes [22] and blowfly salivary gland cells [23] and by injecting IP_3 analogs into fertilized ascidians eggs [24]. Moreover, DT40 cells expressing a mutant IP_3R with reduced sensitivity to Ca^{2+} do not exhibit Ca^{2+} oscillations upon application of cross-linked B-cell receptors [25]. Finally, thimerosal, which sensitizes IP_3R for lower IP_3 levels, potentiates IP_3-induced Ca^{2+} oscillations in sea urchin eggs [26]. These data, together with mathematical models [27, 28], have confirmed that the cross-talk between Ca^{2+} and IP_3 in regulating the IP_3R is critical for generating Ca^{2+} oscillations. However, in Madin-Darby canine kidney epithelial cells [29] and Chinese hamster ovary cells [30–32], each peak of the oscillatory Ca^{2+} signal is preceded by elevated IP_3, as measured by means of a pleckstrin homology domain of PLC-δ_1 tagged with a fluorescent protein indicator. Therefore, it has been proposed that dynamic IP_3 production may produce cytosolic Ca^{2+} oscillations. Nevertheless, other studies using different cells and methods reported opposite conclusions [33–35]. For example, expression of an IP_3 binding domain of IP_3R1 together with two different fluorescent proteins in HeLa cells does not reveal fluctuations in the intracellular IP_3 concentration during Ca^{2+} oscillations [33].

Subtype Specificity of Ca^{2+} Oscillations

Numerous studies using cells endogenously or exogenously expressing single or combined IP_3R subtypes indicate that the subtle distinctions in the properties of each subtype contribute differently to the regulation of cytosolic Ca^{2+} oscillations [3].

Miyakawa et al. [36] first described IP_3R subtype-specific Ca^{2+} oscillations using genetically engineered B cells that express either single or combined IP_3R subtypes. They found that Ca^{2+}-signaling patterns depend on the expression levels of IP_3R subtypes, probably because of their specific response to endogenous modulators, such as IP_3, Ca^{2+} and ATP. IP_3R2 is the most sensitive to IP_3 and is required for robust, long lasting, and regular Ca^{2+} oscillations that occur upon activation of B-cell receptors. IP_3R1 mediates less regular Ca^{2+} oscillations. IP_3R3 is the least sensitive to IP_3 as well as Ca^{2+} and generates only monophasic Ca^{2+} transients. Morel et al. [37] examined the roles of IP_3R1 and IP_3R2 in Ca^{2+} oscillations using vascular myocytes and found that acetylcholine induces Ca^{2+} oscillations in cells expressing both subtypes, and fails to do so in cells expressing only IP_3R1. The oscillations are inhibited by intracellular infusion of heparin, anti-IP_3R2 antibody or antisense oligonucleotides targeting IP_3R2, suggesting that the IP_3R2 subtype is required for acetylcholine-induced Ca^{2+} oscillations in vascular myocytes. Using HeLa cells, which express comparable amounts of IP_3R1 and IP_3R3, Mikoshiba and co-workers showed that knockdown of IP_3R1 terminates Ca^{2+} oscillations, whereas knockdown of IP_3R3 leads to more robust and long lasting Ca^{2+} oscillations [38]. These IP_3R3 knockdown effects were similar in COS-7 cells that predominantly express IP_3R3, suggesting that IP_3R3 functions as an anti Ca^{2+}-oscillatory unit. Almirza et al. reported similar results using normal kidney fibroblasts, which expresses IP_3R1 and IP_3R3 [39]. When IP_3R1 or IP_3R3 are knocked-down, the frequency of prostaglandin $F_{2\alpha}$-induced Ca^{2+} oscillations is significantly decreased or increased, respectively. In NIH-3T3 cells, which predominantly express IP_3R2 and IP_3R3, ATP activates Ca^{2+} oscillations [40]. Ca^{2+} oscillations were induced by application of carbachol in AR4-2J cells, which predominantly expresses IP_3R2, and in HEK293A cells in which both IP_3R1 and IP_3R3 were knocked-down [41]. The contribution of IP_3R2 to Ca^{2+} oscillations is further confirmed by the fact that IP_3-dependent Ca^{2+} oscillations were abolished in osteoclasts of IP_3R2 knockout mice [42]. In rat insulinoma RINm5F cells, which almost exclusively express IP_3R3, application of carbachol or EGF, two agonists that activate PLC through different receptors, or application of IP_3 to permeabilized cells, elicit transient Ca^{2+} release and does not induce Ca^{2+} oscillations [43]. Several reports, including mathematical modeling studies, have indicated that the specific intracellular localization of the IP_3R is crucial for the generation of Ca^{2+} oscillations [44–46]. For instance, Kim et al. [45] found that HL-1 cells derived from mouse cardiac myocytes express both IP_3R1 and IP_3R2. IP_3R1 is expressed diffusely in the perinucleus and IP_3R2 is expressed in the cytosol with a punctuated distribution. Both application of ATP to intact cells and direct introduction of IP_3 into permeabilized cells evoke IP_3-dependent transient intracellular Ca^{2+} release accompanied by Ca^{2+} oscillations. The magnitude of Ca^{2+} oscillations is significantly larger in the cytosol than in the nucleus, while the monophasic Ca^{2+} transient is more pronounced in the nucleus. These results suggest that subtype specificity as well as specific localization of the IP_3R contribute to distinct local Ca^{2+} signaling. Altogether, these data suggest that IP_3R1 and IP_3R2, in particular IP_3R2, crucially contribute in generating Ca^{2+} oscillations, whereas IP_3R3 is an anti-oscillatory unit. Nevertheless, in A7r5 cells derived from rat embryonic thoracic aorta muscle cells, which express IP_3R1 and IP_3R3, knockdown of IP_3R1 only reduces the frequency of arginine vasopressin-induced Ca^{2+} oscillations without affecting the number of cells exhibiting Ca^{2+} oscillations [47]. Moreover, both acetylcholine and cholecystokinin octapeptide activate IP_3R2- and IP_3R3-dependent Ca^{2+} oscillations in pancreatic acinar cells. However, unlike IP_3R2-dependent oscillations, the amplitude of IP_3R3-dependent oscillations decreases throughout the stimulation [48]. The IP_3R subtype-specific Ca^{2+} oscillations are summarized in Table 1.

The IP_3R exists as a homo- or hetero-tetrameric complex to form a functional Ca^{2+} release channel [49–51]. The influence of homo- or hetero-tetrameric channels on intracellular Ca^{2+} oscillations has been investigated. Studies on genetically engineered DT40 cells that express a single IP_3R subtype and therefore a homo-tetrameric receptor demonstrate Ca^{2+} oscillations [36]. Cells with all subtypes, which should at least partially express hetero-tetrameric IP_3Rs, also exhibit Ca^{2+} oscillations [37–43, 45, 47]. Taken together these data suggest that both homo- and hetero-tetrameric IP_3Rs can generate intracellular Ca^{2+} oscillations.

In conclusion, it appears that IP_3R subtype-specific expression crucially shapes cytosolic Ca^{2+} signaling patterns. IP_3R2 is the main pro-oscillatory subtype, whereas IP_3R1 can induce a transient Ca^{2+} signal or an oscillatory Ca^{2+} signal. IP_3R3 mainly shows an anti-oscillatory behavior, but could underlie short-term oscillations depending on the cell type and stimulus. Further characterization of homo- and hetero-tetrameric IP_3R-dependent Ca^{2+} oscillations are needed for fully understanding the intricacies of each IP_3R subunit in shaping Ca^{2+} oscillations.

Table 1 The occurrence of Ca^{2+} oscillations and the expression of the different IP_3R subtypes

Cell type	IP_3R1	IP_3R2	IP_3R3	Activator	Ca^{2+} oscillations	Reference
DT40	+	−	−	B cell receptor	↑	[36]
DT40	−	+	−	B cell receptor	↑	[36]
DT40	−	−	+	B cell receptor	↓	[36]
Vascular myocytes	+	+	−	Acetylcholine	↑	[37]
Vascular myocytes	+	−	−	Acetylcholine	↓	[37]
HeLa	++	+	++ (kd)	ATP	↑	[38]
HeLa	++ (kd)	+	++	ATP	↓	[38]
COS-7	+	+	++ (kd)	ATP	↑	[38]
NRK	+	−	+ (kd)	Prostaglandin $F_{2\alpha}$	↑	[39]
NRK	+ (kd)	−	+	Prostaglandin $F_{2\alpha}$	↓	[39]
NIH-3T3	+	++	++	ATP	↑	[40]
AR4-2 J	+	++	+	IGF-1	↑	[41]
HEK293A	+ (kd)	+	+ (kd)	Carbachol	↑	[41]
Osteoclasts	+	+	+	RANKL	↑	[42]
Osteoclasts	+	−	+	RANKL	↓	[42]
Osteoclasts	+	−	−	RANKL	↓	[42]
RINm5F	±	±	++	Carbachol, EGF, IP_3	↓	[43]
HL-1	+	+	−	ATP	↑	[45]
A7r5	+ (kd)	−	+	Arginine vasopressin	↓	[47]
Pancreatic acinar cells	+	+	+	Acetylcholine, CCK-OP	↑	[48]
Pancreatic acinar cells	+	−	+	Acetylcholine, CCK-OP	↑	[48]

+ high expression, − low expression, and kd, knock down or low expression

Subtype Specificity of IP_3-Binding Affinity to IP_3R

As summarized earlier, cytosolic Ca^{2+} oscillations are IP_3R subtype-dependent. IP_3 and Ca^{2+} are the two key modulators of IP_3R and the distinct subtype properties determine the diverse regulatory effects. Each subtype has different IP_3 binding affinity. Sudhof et al. were first to report, using an equilibrium IP_3 binding assay, that the order of IP_3-binding affinity was $IP_3R2 > IP_3R1 > IP_3R3$ [9, 52]. Applying the same method, Wojcikiewicz et al. [53] and Nerou et al. [54] later claimed a different order, $IP_3R1 > IP_3R2 > IP_3R3$. Mikoshiba and co-workers performed a detailed molecular analysis of the IP_3 binding affinity of all three subtypes [11, 13]. They found that the IP_3-binding affinities of purified IP_3-binding domains are close to the intrinsic IP_3-binding affinity of all three IP_3R subtypes, and describe the following order $IP_3R2 > IP_3R1 > IP_3R3$. They also showed that IP_3-binding core fragments, which do not contain the ligand coupling/suppressor domain, display an almost identical IP_3-binding affinity for all three subtypes. By a serious and compelling molecular analysis, they concluded that the functional diversity in ligand sensitivity among IP_3R subtypes arises from structural differences in the ligand coupling/suppressor domain, which attenuate the IP_3-binding affinity of the IP_3-binding core domain through an intramolecular mechanism. Tu et al. recorded single-channel activities of the recombinant IP_3R1, IP_3R2, and IP_3R3 reconstituted into planar lipid bilayers [55]. This report had a similar conclusion with IP_3R2 showing the highest apparent IP_3-affinity, followed by IP_3R1, and then by IP_3R3.

Differences amongst IP_3R subtypes in terms of IP_3-binding affinities do not reflect intrinsic differences in the properties of the channels to regulate Ca^{2+} oscillations. Instead differences in the state of phosphorylation and/or association with interacting proteins exist. Nevertheless, IP_3R1 and IP_3R2 are most sensitive to IP_3, a property that could contribute in their function as Ca^{2+} oscillatory unit. The exact contribution of subtype specific IP_3-binding affinities on Ca^{2+} oscillations remains to be further investigated.

Subtype Specificity of Ca^{2+} Inhibition and Induction

As mentioned earlier, repeated activation and inhibition of IICR by fluctuating cytosolic Ca^{2+} levels have been proposed as central molecular mechanisms for IP_3R-dependent Ca^{2+} oscillations [56]. Several stimulatory and inhibitory Ca^{2+} binding sites on the IP_3R have been identified and characterized. For instance, two sites are localized in the

IP_3 binding core and another site is located close to the transmembrane domain [57], exemplifying the complex synergy between IP_3 and Ca^{2+} in the regulation of the IICR [12]. Ca^{2+} regulation of IP_3R activity may result in changed IP_3 binding affinity, alteration of channel open probability, or indirect influence on IP_3R associated proteins, such as the CaM. Interestingly, this can occur specifically on one IP_3R subtype, making Ca^{2+} regulation of IICR one of the major mechanisms to produce versatile signals, as confirmed by mathematical modeling studies [58].

The complex regulation of the IP_3R subtypes′ activity by Ca^{2+} has been recently reviewed in detail [3] and we will therefore mainly focus on how Ca^{2+} itself modulates Ca^{2+} oscillations. Everyone in the field agrees that all three subtypes are activated by Ca^{2+}. Inhibition of the IP_3R by Ca^{2+}, however, is more controversial. In single channel studies, each subtype is inhibited by high Ca^{2+} concentrations, even though the threshold and speed of inhibition differs [3]. Moreover, Ca^{2+} inhibition of IICR sometimes depends on the addition of an extra factor, for example ATP for IP_3R3 [55]. Therefore, all three subtypes can potentially support Ca^{2+} oscillations based on the model described previously, where concerted actions of IP_3 and Ca^{2+} stimulates IP_3R. Accordingly, IP_3R1-, IP_3R2-, and IP_3R3-dependent Ca^{2+} oscillations have been observed, although IP_3R3-dependent Ca^{2+} oscillations are less likely to occur and are also less frequently observed (see previous sections).

In most cases, cells express more than one IP_3R subtype. Interestingly, when several IP_3R subtypes are expressed, one of them becomes dominant regarding Ca^{2+} regulation of IICR [36]. This result also calls for caution when drawing conclusions on the subtype specificity of Ca^{2+} signaling, since expression of even a small amount of one subtype could critically affect the Ca^{2+} signaling pattern [59].

Taken together, Ca^{2+} activation and inhibition properties of IP_3R1 and IP_3R2 make them likely to support Ca^{2+} oscillations in physiological conditions [60], whereas specific cellular circumstances are required for activation of IP_3R3-dependent Ca^{2+} oscillations.

Subtype Specificity of Phosphorylation of IP_3R

Phosphorylation of the IP_3R is involved in many Ca^{2+} signaling pathways [61] and the different subtypes are interacting with protein kinases and phosphatases differently [62]. Many of the phosphorylation sites are subtype-specific, increasing the diversity in regulatory fine tuning of Ca^{2+} oscillations. The functional consequences of these regulatory modifications are only partially understood, and in some cases remain controversial. Therefore we will here focus on those protein kinases known to modulate Ca^{2+} oscillations through phosphorylation of IP_3R.

PKA-dependent phosphorylation of IP_3R has been demonstrated extensively. Phosphomimetic mutations of IP_3R1 expressed in DT40 cells showed that PKA-mediated phosphorylation decreases the threshold for Ca^{2+} oscillations, without affecting the amplitude or frequency [63]. PKA phosphorylates two distinct sites in IP_3R1 internal coupling domain (S1588 and S1755) [64]. Although these sites are not conserved in IP_3R2 and IP_3R3, PKA-dependent phosphorylation of these subtypes has been demonstrated [65]. In parotid acinar cells [66] and the pancreatic AR4-2J cell line [67], PKA directly phosphorylates IP_3R2, dramatically potentiating Ca^{2+} release. Interestingly, raising cAMP during sub-threshold agonist stimulation resulted in an oscillatory Ca^{2+} signal, while raising cAMP during an Ca^{2+} oscillation converted the response into a peak and plateau-like signal [66], probably because of a shift in the concentration dependency in IICR. CaMKII has been proposed to be involved in the control of the Ca^{2+}-dependent regulation of IICR and in the occurrence of Ca^{2+} oscillations [68]. The most extensive information regarding CaMKII regulation of IP_3R is derived from studies performed on IP_3R2 [69, 70], which is the predominant subtype in cardiac ventricular myocytes. CaMKII-dependent phosphorylation significantly decreased the open probability of IP_3R2 in lipid bilayers, which suggests a Ca^{2+}-dependent negative feedback mechanism on IP_3R2 activity in the cardiomyocyte nuclear envelope [71]. This may also result in a Ca^{2+}-dependent inhibitory loop of Ca^{2+} oscillations [72]. Functional effects of PKC-mediated phosphorylation of the IP_3R were first studied in isolated rat liver nuclei [73]. PKC-mediated phosphorylation of IP_3R1 in vitro is in addition regulated by Ca^{2+} and CaM [74]. As both Ca^{2+} and CaM inhibit the PKC-mediated phosphorylation of IP_3R1, it is possible that this process may contribute to the negative slope of the Ca^{2+}-dependent bell-shaped regulation of IP_3R by Ca^{2+}, consequently affecting Ca^{2+} oscillations. Recent demonstrations suggest a role for PKC-mediated phosphorylation of IP_3R2 [75] and IP_3R3 [43]. These reports show that when IP_3R2 or IP_3R3 are phosphorylated by PKC, IP_3-dependent Ca^{2+} oscillations are decreased in cells expressing only those subtypes. Thus, PKC may act as a subtype specific regulator of IP_3R-mediated cytosolic Ca^{2+} oscillations. These differences are not unexpected since IP_3R subtypes possess different potential phosphorylation sites [43, 76]. How phosphorylation of IP_3R subtypes by distinct protein kinases affect Ca^{2+} oscillations are summarized in Table 2.

The subtype specific regulation of IP_3R by phosphorylation and its relation to Ca^{2+} oscillations are not fully understood. These processes are likely to be dependent on specific IP_3R subtypes expression levels and protein kinases activation, and need to be further investigated.

Table 2 The IP_3R subtype specificity of protein kinases and IP_3R-associated proteins and their modulating effects on Ca^{2+} oscillations

Effect	Stimulatory			Inhibitory		
Effectors	IP_3R1	IP_3R2	IP_3R3	IP_3R1	IP_3R2	IP_3R3
PKC	[73, 74]	–	–	–	[75]	[43]
PKA	[63]	[67]	–	–	[67]	–
CaMKII	–	–	–	[68][72]	–	–
CaBP1	–	–	–	[82]	–	[82]
Na,K-ATPase	[83, 84]	[83, 84]	[83, 84]	–	–	–
IRBIT	–	–	–	[85]	–	–
AKAP9	[87]	–	–	–	–	–
PS1/PS2	[88, 89]	[88, 89]	[88, 89]	–	–	–
ERp44	–	–	–	[90]	–	–
GRP78	[91]	–	–	–	–	–
Bcl-2	[78, 92, 94, 96]	[78, 92, 94, 96]	[78, 92, 94, 96]	[97]	[97]	[97]
Bcl-X_L	[93, 95]	[93, 95]	[93, 95]	–	–	–
Mcl-1	[78]	[78]	[78]	–	–	–
Cytochrome C	[98, 99]	–	–	–	–	–
GIT1/GIT2	–	–	–	[81]	[81]	[81]
NCS-1	[80, 100]	[80, 100]	[80, 100]	–	–	–

Regulation of IP_3R Activity by Accessory Proteins

About forty proteins have been reported to interact with IP_3R, most of which modulate IP_3R channel activity [1, 3, 77–81]. There is a lack of data regarding IP_3R2 and IP_3R3 specific binding proteins since most of these proteins are identified by co-immunoprecipitation studies with one or two IP_3R subtypes or using IP_3R1 probes. Few reports show that some of these associated proteins modulate Ca^{2+} oscillations differently. Therefore, we summarize here the proteins that bind to IP_3R and modulate Ca^{2+} oscillations, whether they bind to a specific IP_3R subtype or not (Table 2; Fig. 1).

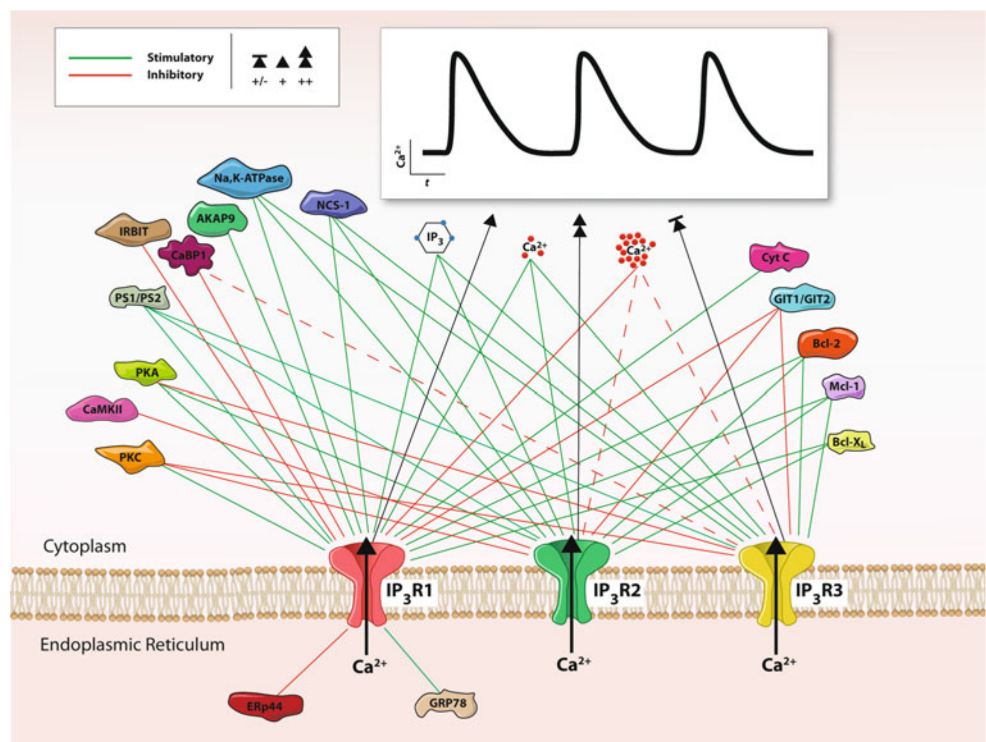

Fig. 1 Cartoon illustrating the three IP_3R subtypes (IP_3R1, IP_3R2, and IP_3R3) and related protein kinases and interacting proteins involved in the regulation of cytosolic Ca^{2+} oscillations

CaBP1, one of the neuronal Ca^{2+} binding proteins, was co-immunoprecipitated with IP_3R1 and IP_3R3 [82]. The CaBP1-binding site was mapped in the ligand coupling/suppressor domain of IP_3R1. This interaction functionally inhibits IP_3-dependent Ca^{2+} oscillations in COS-7 cells expressing CaBP1, in permeabilized COS-7 cells exposed to recombinant CaBP1, and in *Xenopus* oocytes injected with recombinant CaBP1.

Na,K-ATPase, a plasma membrane ion pump, directly binds to the IP_3 binding-domain of all three IP_3R subtypes through its NH_2-terminal tail [83, 84]. In the presence of ouabain, Na,K-ATPase triggers IP_3-dependent Ca^{2+} oscillations in COS-7 cells and in primary culture of rat renal proximal tubule cells. Overexpression of a peptide corresponding to the wild type NH_2-terminal tail of Na,K-ATPase decreased the number of cells exhibiting Ca^{2+} oscillations, an effect not observed when a mutant type that does not bind to IP_3R was used.

IRBIT was identified to bind to the IP_3 binding core of IP_3R1 [85]. This interaction suppresses the activation of IP_3R by regulating the IP_3 sensitivity of IP_3R1. Knockdown of IRBIT in HeLa cells increases ATP-induced cytosolic Ca^{2+} oscillations.

AKAP9, one of the neuronal PKA-anchoring adaptor proteins, binds to the leucine/isoleucine zipper (LIZ) motif in the internal coupling domain of IP_3R1 [86]. Expression of a 36-residues LIZ fragment, which can disrupt the IP_3R1-AKAP9 association, reduces the frequency of Ca^{2+} oscillations induced by application of dopamine in primary culture of medium spiny neuron [87].

Presenilins (PS), including PS1 and PS2, are proteins bound to the gamma-secretase protease complex. Mutations in the genes encoding PS1 and PS2 are the major cause of familial Alzheimer's disease (FAD). Wildtype and FAD-mutants of PS1 and PS2 have been co-immunoprecipitated with IP_3R1 and IP_3R3 [88, 89]. These interactions exert profound stimulatory effects on the IP_3R gating activity. Mutated PSs were demonstrated to increase frequency of both spontaneous Ca^{2+} oscillations and Ca^{2+} oscillations triggered by cross-linking the B cell receptor with IgM antibody in both DT40 cells and FAD patient B cells.

ERp44 is an ER lumenal protein of the thioredoxin family. Depending on the oxidative status in the ER lumen, it can interact directly with the third IP_3R1 lumenal loop and inhibit its activity [90]. Knockdown of ERp44 in HeLa cells increases ATP-triggered cytosolic Ca^{2+} oscillations.

GRP78, another ER lumenal protein, also interacts with the third lumenal loop of the IP_3R1 [91]. In contrast to ERp44, GRP78 enhances IP_3R1 channel activity. Knockdown of GRP78 in HeLa cells decreases ATP-triggered Ca^{2+} oscillations, which is restored by re-expression of the protein.

Bcl-2, Bcl-X_L, and Mcl-1, three anti-apoptotic proteins that belong to Bcl-2 family, have been reported to bind to the CTT and/or the internal coupling domain of all three IP_3R subtypes [78, 92–95]. Bcl-2 enhances IP_3-mediated Ca^{2+} oscillations induced by T cell receptor activation in WEHI7.2 cells, Jurkat cells, and wild type DT40 cells [78, 92, 94, 96], whereas Ca^{2+} oscillations induced by serum withdrawal in NIH-3T3 murine fibroblasts are dampened [97]. Expression of Bcl-X_L in wild type DT40 cells or in DT40 cells engineered to express each IP_3R subtype increases the number of the cells exhibiting Ca^{2+} oscillations as well as the oscillatory frequency [93, 95]. Interaction of Mcl-1 with IP_3R increases the number of DT40 cells exhibiting anti-B cell receptor antibody induced Ca^{2+} oscillations [78]. Bcl-2 and Mcl-1 also increase the number of cells exhibiting Ca^{2+} oscillations and the amplitude and/or the frequency of spontaneous Ca^{2+} oscillations in DT 40 cells [78].

Cytochrome C, one of the key components of the apoptotic cascade, was found to selectively and directly bind to IP_3R1 CTT during early apoptosis via a cluster of glutamic acid residues (binding to IP_3R2 and IP_3R3 were not confirmed), resulting in staurosporine-induced sustained Ca^{2+} oscillations [98, 99].

G-protein-coupled receptor kinase-interacting proteins (GIT), including GIT1 and GIT2, bind to the CTT of all three IP_3R subtypes, but have stronger binding affinity to IP_3R2 (more than 10- and 20-fold as compared to IP_3R1 and IP_3R3, respectively), and inhibit IICR [81]. Knockdown of GIT proteins in HeLa or COS-7 cells increases the number of cells exhibiting Ca^{2+} oscillations.

Neuronal Ca^{2+} sensor 1 (NCS-1), a Ca^{2+} binding protein whose expression could be enhanced by application of Taxol, a natural product for the treatment of solid tumors, was co-immunoprecipitated with all three subtypes of IP_3R [80, 100]. The NCS-1-IP_3R interaction increases the number of cells exhibiting IP_3R-dependent Ca^{2+} oscillations in SH-SY5Y human neuroblastoma cells [100] and the frequency of spontaneous Ca^{2+} oscillations in rat ventricular cardiomyocytes [80].

The diversity in distribution of associated proteins and/or IP_3R subtypes is essential for the versatility of IP_3R subtype-dependent Ca^{2+} oscillations in different cell types. More information, however, is required for determining the individual role of each separate subtype in modulating cytosolic Ca^{2+} oscillations.

Conclusion and Future Directions

It is evident that the different IP_3R subtypes are regulated by a large number of cellular mechanisms that varies in a cell type-specific manner. In this review we have focused on IP_3R subtype-specific modulation of Ca^{2+} oscillations. Ca^{2+} oscillations are repetitive increases in the cytosolic

Ca^{2+} concentration that are used by the cell to convey information within or between cells. The oscillatory Ca^{2+} signal is known to be initiated at the onset of fertilization [101–103] and to continue throughout life to control a vast array of cellular processes as diverse as proliferation, differentiation, development, learning and memory, contraction, secretion, and cell death [1, 15]. Altered intracellular Ca^{2+} signaling has been linked to many diseases, such as Hungtington's, Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis, schizophrenia, spinocerebellar ataxias, heart failure, polycystic kidney disease, and human immunodeficiency virus infection [104–107]. It is therefore essential to determine the molecular mechanisms involved in the generation of intracellular Ca^{2+} oscillations. Additionally, Ca^{2+} oscillations are known to encode information in their frequency and amplitude to activate various specific downstream targets [15–17]. Efforts to understand the nature of these "cellular radio signals" started at the same time as Ca^{2+} oscillations were discovered and have resulted in a large number of publications [16–18, 22, 28, 30, 32, 35, 37, 39, 42, 47, 56, 60, 83, 100–102], most of which is cell type- and agonist-specific. To determine the associations between (1) stimulus, (2) Ca^{2+} oscillation, and (3) activation of a specific downstream cellular process, future studies will have to consider the molecular partners involved in each step. The recent rapid development of sophisticated molecular and genetic tools, such as small interfering RNA [108] and optogenetics [109], will surely advance our future knowledge about IP_3R subtype-specific regulation of Ca^{2+} oscillations.

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