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Review

Regulation of inositol 1,4,5-trisphosphate-induced Ca^{2+} release by reversible phosphorylation and dephosphorylation

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ABSTRACT

The inositol 1,4,5-trisphosphate (IP_3) receptor (IP_3R) is a universal intracellular Ca^{2+}-release channel. It is activated after cell stimulation and plays a crucial role in the initiation and propagation of the complex spatio-temporal Ca^{2+} signals that control cellular processes as different as fertilization, cell division, cell migration, differentiation, metabolism, muscle contraction, secretion, neuronal processing, and ultimately cell death. To achieve these various functions, often in a single cell, exquisite control of the Ca^{2+} release is needed. This review aims to highlight how protein kinases and protein phosphatases can interact with the IP_3R or with associated proteins and so provide a large potential for fine tuning the Ca^{2+}-release activity and for creating efficient Ca^{2+} signals in subcellular microdomains.

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1. Introduction

It becomes increasingly clear that intracellular Ca^{2+} signals controlling many vital cellular processes are confined to subcellular microdomains. The molecular architecture of such microdomains is a matter of intense investigation but is as yet still poorly understood. Phosphorylation/dephosphorylation of the inositol 1,4,5-trisphosphate (IP_3) receptor (IP_3R) and/or of associated proteins seems however to play a crucial role. The IP_3R was found to be a substrate for a wide variety of different protein kinases and phosphatases and there is a very large number of in silico predicted consensus sites for phosphorylation as well as for docking of kinases and/or of their anchoring proteins. Given the fact that many of these sites are differentially present in the various IP_3R isoforms, this diversity opens a huge potential for regulatory fine tuning of Ca^{2+} release and signaling. Phosphorylation of the IP_3R is involved in many Ca^{2+}-signaling pathways linked to important cellular functions ranging from oocyte maturation to cell death. It is therefore our aim to present a comprehensive state-of-the-art review on the topic, and to indicate a number of issues that need further investigation.

2. The inositol 1,4,5-trisphosphate receptor

Cell activation by extracellular agonists as hormones, growth factors and neurotransmitters often leads to phospholipase-C (PLC) activation and subsequent intracellular IP_3 production. IP_3 diffuses through the cytoplasm until it binds and activates its receptor. This IP_3R is an intracellular Ca^{2+}-release channel predominantly located on the endoplasmic reticulum (ER) and responsible for a controlled release of Ca^{2+} ions in the cytoplasm, which is crucial for setting up complex spatio-temporal Ca^{2+} signals [1,2].

The functional IP_3R/Ca^{2+}-release channel is a tetramer. The four subunits have a similar general structure, but IP_3R diversity is created in higher organisms by (i) the presence of 3 genes (ITPR1, ITPR2 and ITPR3) encoding for IP_3R1, -2 and 3 resp., (ii) the occurrence of splicing events, and (iii) the possible formation of homo- and heterotetramers [3]. Each subunit consists of about 2700 a.a., and the functional Ca^{2+}-release channel therefore has a molecular mass of around 1.2 MDa. The linear sequence of the IP_3R consists of three large regions, an N-terminally located IP_3-binding region of about 600 a.a., a large modulatory and transducing region (about 1600 a.a.) and a small

Abbreviations: a.a., amino acids; AHCY, S-adenosyl-L-homocysteine hydrolase; Bcl-2, B-cell lymphoma-2; BCR, B-cell receptor; BH, Bcl-2 homology; CaM, calmodulin; CaMKII, Ca^{2+}/CaM-dependent protein kinase; CDK, cyclin-dependent kinase; DAG, diacylglycerol; ER, endoplasmic reticulum; ERK, extracellular-signal regulated kinase; FKBP, FK506-binding protein; IICR, IP_3-induced Ca^{2+} release; IP_3, inositol 1,4,5-trisphosphate; IP_3R, IP3 receptor; IRAG, IP_3R-associated cGMP kinase substrate; IRBIT, IP_3R-binding protein released by IP_3; JNK, Jun N-terminal kinase; MAP kinase, mitogen-activated protein kinase; MPM2, mitotic protein monoclonal 2; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; PKG, protein kinase G; PLC, phospholipase C; PLK, polo-like kinase; PP, protein phosphatase; RACK, receptor for activated C kinase; TCR, T-cell receptor

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C-terminal region (about 500 a.a.) containing the 6 transmembrane domains. More recently, it has been shown that the N-terminal IP_3-binding region is composed of a suppressor domain and an IP_3-binding core, while the C-terminal region is composed of a channel region and a coupling region (Fig. 1) [4]. Most work has been performed on the ubiquitously expressed IP_3R1, but it is assumed that the various isoforms have the same general structure. In spite of their similarity, it is however clear that the various IP_3R isoforms can subtly differ in their properties. Their affinity for IP_3 displays a rank-order $IP_3R2 > IP_3R1 > IP_3R3$ [5,6], which seems predominantly due to differences at the level of the suppressor domains [7]. Additionally, differences in sensitivity for regulatory factors as e.g. Ca^{2+}, ATP and redox status were observed [5,8-15].

Cryo-electron-microscopy analysis demonstrated that IP_3R1, and the other isoforms probably as well, has a quite open structure [16] allowing easy access of regulatory proteins to various sites on the IP_3R. In addition, the IP_3R structure undergoes major conformational changes under influence of Ca^{2+} [17]. Hence, many proteins can directly interact with the IP_3R, some of them at least in a conformation- or isoform-specific way [3,18,19].

The physiological relevance of the existence of multiple IP_3R isoforms is reflected in the fact that they are expressed differently and at varying subcellular localizations in the different cell types and organs [20] and that their expression pattern changes during cellular differentiation and development as well as under patho(physio) logical situations [3].

Not unexpectedly, the IP_3R isoforms contain on their sequences multiple phosphorylation consensus sites and many docking sites for protein kinases and phosphatases. Today at least 12 different protein kinases are known to directly phosphorylate the IP_3R. This, combined with the fact that some important regulatory proteins associated with the IP_3R (IRBIT, see part 3, and Bcl-2, see part 4) are themselves regulated by phosphorylation and/or can bind protein kinases or phosphatases, makes the understanding of the regulation of the IP_3R by phosphorylation/dephosphorylation even more complex and the functional consequences of this regulation are still only partially understood.

3. IRBIT, the IP_3R-binding protein released by IP_3, and its role in regulating the phosphorylation status of IP_3R

3.1. Structure of IRBIT

IRBIT, the IP_3R-binding protein released by IP_3, corresponds to the S-adenosyl-L-homocysteine hydrolase (AHCY)-like protein AHCYL1 (also termed DCAL, dendritic cell-expressed AHCY-like protein) and is composed of a specific N-terminal IRBIT domain and a C-terminal AHCY domain [21,22].

The AHCY domain of IRBIT closely resembles AHCY but contains critical mutations (V^{256} and V^{450} instead of T^{158} and H^{353} resp., see Fig. 2) and does not demonstrate any form of adenosylhomocysteine-hydrolase activity [23]. It contains a PDZ-ligand that mediates an IP_3-insensitive interaction with the IP_3R [24]. In contrast herewith the IRBIT domain enables binding to the IP_3R in a way that can be competed by IP_3 and additionally contains a protein phosphatase (PP) 1 docking site, several phosphorylation sites and a PEST motif (a.a. 65 to 92) that targets the domain for proteolytic degradation (Fig. 2).

IRBIT was discovered as a ubiquitous protein with its highest expression levels in neuronal tissue and the possibility to interact with and to inhibit IP_3R1, -2 and -3 [21]. During early embryogenesis, its expression is tightly regulated; its microinjection in zebrafish embryos results in a dorsalized phenotype that is similar to the results of pharmacological inhibition of the IP_3R [25,26].

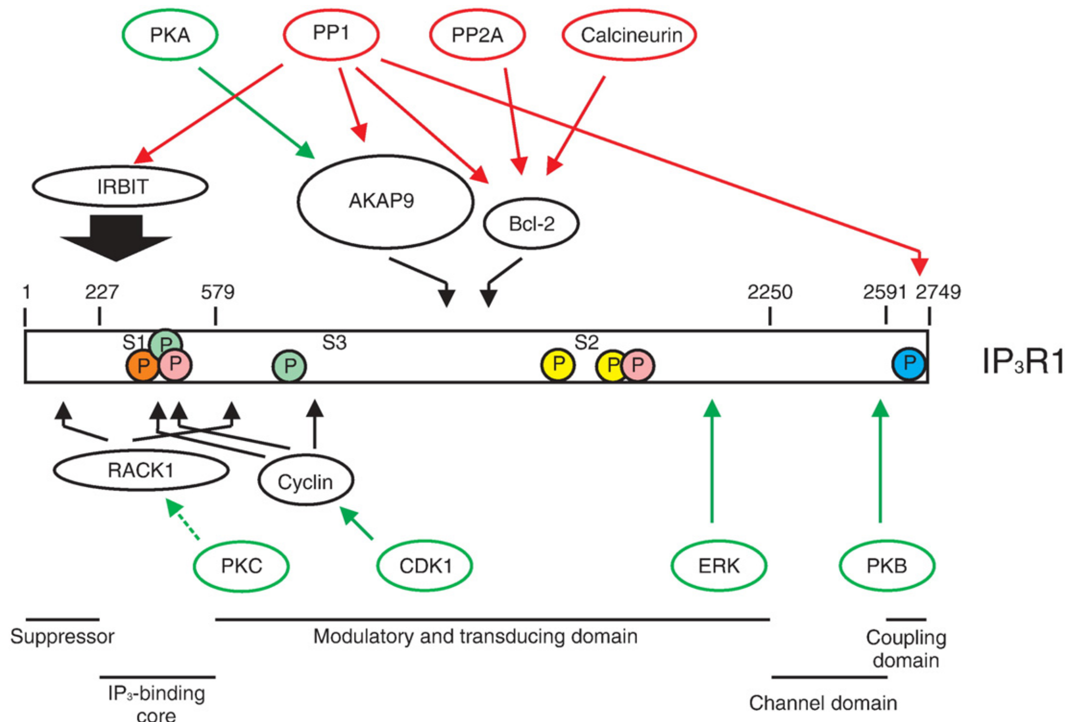

Fig. 1. The structure of the IP_3R1/Ca^{2+}-release channel showing the proteins and the sites involved in its regulation by phosphorylation/dephosphorylation. The various functional domains are indicated at the bottom of the figure [4]. Splice sites (S1, S2 and S3) are indicated. Docking proteins (black), protein kinases (green) and protein phosphatases (red) are shown with their identified interaction sites on IP_3R1. The interaction of IRBIT (broad arrow) with the IP_3R stretches over the complete IP_3-binding core, and may encompass the suppressor domain as well. The coupling of PKC via RACK1 has not yet been described and is therefore indicated by a dotted line. Proteins of which the interaction site with the IP_3R1 has not yet been determined with certainty are not shown. Identified phosphorylation sites are shown in yellow (phosphorylation by PKA/PKG), blue (by PKB), pale green (by CDK1), pink (by ERK) and orange (by Fyn). For more details, please see text.

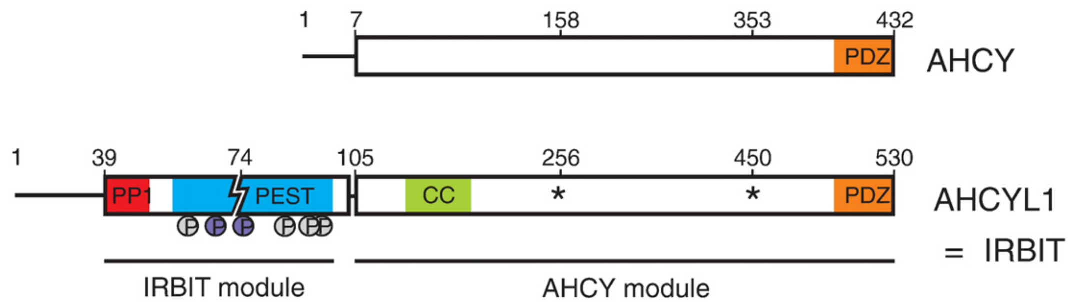

Fig. 2. The modular structure of AHCY and IRBIT (AHCYL1). IRBIT contains a C-terminal AHCY domain that is preceded by the specific IRBIT domain. The AHCY domain of IRBIT contains a conserved PDZ ligand (orange), but has no enzymatic AHCY activity due to mutations of T^{158} and H^{353} to two valine residues (V^{256} and V^{450}, indicated by asterisks). In contrast with AHCY, it also contains a coiled-coil region (CC, green). The IRBIT domain is composed of a PP1-binding site (PP1, red) followed by a PEST-motif (PEST, blue) that can be cleaved and that contains several phosphorylation sites: phosphorylation of S^{68} (grey circle) by an unidentified Ca^{2+}-activated kinase allows subsequent phosphorylation of S^{71} and S^{74} by CK1 (purple circles), while the protein kinases involved in the phosphorylation of T^{82}, S^{84} and S^{85} (grey circles) are also not yet identified.

3.2. Regulation of the IRBIT domain via (de)phosphorylation

The interaction of IRBIT with the IP_3R is dependent on phosphorylation of the IRBIT domain and occurs directly, without the need for adaptor proteins [24]. The critical phosphorylation sites reside within the PEST motif, where phosphorylation of S^{68} allows for subsequent phosphorylation of S^{71} and S^{74} by casein kinase (CK) 1 [27,28]. The latter two phosphorylations are both necessary and sufficient to enable IRBIT to bind to and inhibit the IP_3R [27]. The identity of the protein kinase that in vivo phosphorylates S^{68} remains to be elucidated but interestingly all five candidates that are predicted from in silico analysis (protein kinase D, Ca^{2+}/CaM-dependent protein kinase II (CaMKII) and IV, AMP-activated protein kinase and mitogen-activated protein kinase (MAP kinase)-activated protein kinase 2) are Ca^{2+}-activated protein kinases [27]. The functional relevance of the three other phosphorylation sites (T^{82}, S^{84} and S^{85} [29]) is not known, but they could either enhance the phosphorylation-dependent interaction of IRBIT with its targets, or alternatively, be a way to target IRBIT to different interaction partners.

The IRBIT domain is inactivated by dephosphorylation. PP1 has previously been shown in complex with the IP_3R via both a direct interaction with the C-terminal tail of the IP_3R [30], and an indirect interaction via the large scaffold protein AKAP9 [31] (Fig. 1). We recently showed that PP1 also binds directly to the IRBIT domain, whereby the so-called RVXF motif, [R/K]-X_{0-1}-[I/V]-{P}-F, functions as the docking site ({P} indicates any a.a. except proline) [27]. PP1 specifically dephosphorylates S^{68}, but neither S^{71} nor S^{74}. Noteworthy, the dephosphorylation of S^{68} is strictly dependent on the direct interaction between PP1 and the IRBIT domain [27]. It also prevents the subsequent CK1-mediated phosphorylation of S^{71} and S^{74}, and hence the activation of the IRBIT domain. Inversely, inactivation of the PP1 docking site increases the interaction of IRBIT with the IP_3R [27]. The protein phosphatase(s) that dephosphorylate(s) S^{71} and S^{74} remain(s) elusive. It is also still unknown whether IRBIT-bound PP1 can affect the phosphorylation state of the IP_3R.

The importance of the phosphorylation sites on the IRBIT domain is underscored by the fact that IRBIT can in vivo be cleaved inside the PEST domain, between the two CK1-dependent phosphorylation sites (Fig. 2) [24,27]. This proteolytic cleavage represents an irreversible way to inactivate the IRBIT domain, as neither IRBIT[1-73] nor IRBIT [74-530] can bind to the IP_3R [24]. Inactivation of IRBIT by proteolytic cleavage and subsequent removal of the endogenous attenuation of IP_3-induced Ca^{2+} release (IICR) could therefore play a role in death-signaling pathways [32].

3.3. Phosphorylated IRBIT inhibits the IP_3R

When IRBIT is phosphorylated on S^{71} and S^{74}, it can bind to the IP_3R [27]. Both IRBIT and IP_3 bind to largely overlapping sites in the N-terminal region of the IP_3R [24,28]. Their binding sites are however not completely identical: mutation of R^{265} or T^{267} in the IP_3R disables the binding of IP_3, but not of IRBIT [28]. Additionally, the suppressor domain of the IP_3R may be involved in the binding of IRBIT [24] (Fig. 1). Binding experiments demonstrated that phosphorylated IRBIT, purified from Sf9 cells, has a ~10-fold lower affinity for the IP_3R than IP_3 (IC_{50} ~250 nM versus ~26 nM) [24] which is however still significantly higher than the affinity of other regulatory proteins interacting with the IP_3R as e.g. calmodulin (CaM; IC_{50} ~2 μM [33,34]).

Though both IRBIT and IP_3 interact with the IP_3-binding core, the former is unable to activate the IP_3R channel [28]. Moreover, binding of phosphorylated IRBIT competes with the IP_3 needed for activating the IP_3R and for subsequent IICR [27]. This explains why phosphorylated IRBIT reduces IICR in permeabilized fibroblasts and why this effect can be overcome at high IP_3 concentrations [24]. Similar results were also observed in mouse cerebellar microsomes but overexpression of IRBIT appeared not to affect IICR in intact HeLa cells [28]. This could be due to high endogenous levels of IRBIT and/or of its close homologue AHCYL2. Inversely, silencing of IRBIT increased the number of HeLa cells that responded to low levels of IP_3 [28].

Overall, the functional in vivo role of IRBIT on the IP_3R remains puzzling and the observed effects are disappointingly small. This could point to an additional cellular regulatory mechanism that controls its activity. In this respect, it should be noted that pH could be an important regulator of the interaction of the IRBIT domain with its targets. We observed that an increase in pH decreases IRBIT binding to the IP_3R, while it increases the binding of IP_3 [24]. Competition between IRBIT and IP_3 is therefore extremely dependent on intracellular pH. Hence, it is possible that in vivo effects of IRBIT on the IP_3R can only be clearly observed in conditions of a (locally) decreased intracellular pH. As IRBIT also targets Na^+/HCO_3^- cotransporters [35] it might constitute a link between intracellular pH regulation and Ca^{2+} signaling [22].

4. The anti-apoptotic Bcl-2 protein and its role in regulating the phosphorylation status of IP_3R

4.1. Structure and function of Bcl-2

Bcl-2 (B-cell lymphoma-2) is the prototype of a large family of pro-apoptotic and anti-apoptotic proteins, characterized by one or more specific domains, called Bcl-2 homology (BH) domains. Bcl-2 contains four BH domains and appears embedded in the ER, nuclear envelope and outer mitochondrial membrane via its hydrophobic C-terminal tail [36]. Bcl-2 as well as other anti-apoptotic members of the Bcl-2 family, such as Bcl-Xl, can inhibit the multidomain pro-apoptotic Bcl-2-family members Bax and Bak that lack the BH4 domain. Activated Bax and Bak normally translocate to the mitochondria and oligomerize, thereby leading to mitochondrial outer-membrane

permeabilization and cytochrome-c release, and ultimately to cell blebbing and removal. In addition, the hydrophobic groove formed by BH domains 1–3 in as well the anti-apoptotic Bcl-2/Bcl-Xl as the pro-apoptotic Bax/Bak can bind the amphipatic BH3 domain of the so-called BH3-only pro-apoptotic proteins [36].

Besides this role at the level of the mitochondrial outer membrane, many Bcl-2-family members seem to play a crucial role in controlling the Ca^{2+} content of the ER and/or the Ca^{2+} release from it [37]. Although it is still not clear how regulation of intracellular Ca^{2+} homeostasis by the anti-apoptotic Bcl-2-family members is exactly achieved, it is clear that IP_3Rs hereby play a central role [38]. Recent evidence demonstrated a binding site for Bcl-2 in the regulatory region of the IP_3R (Fig. 1) [39], while previous evidence indicated that the related protein Bcl-Xl would bind in the C-terminal region [40]. Both Bcl-2 and Bcl-Xl seem to be able to interact with all three IP_3R isoforms [40,41], though isoform-specific effects have been described, at least for Bcl-Xl [42]. The exact relation between the various IP_3R isoforms, Bcl-2/Bcl-Xl and their proposed binding sites remains however to be further investigated. Interestingly, the anti-apoptotic Bcl-2-family members display a dual role on Ca^{2+} signaling. At low levels of cellular activation Bcl-2 and Bcl-Xl seem in lymphocytes so to enhance pro-survival Ca^{2+} oscillations, thereby stimulating dephosphorylation of the nuclear factor of activated T cells (NFAT) and mitochondrial bioenergetics, whereas they would inhibit pro-apoptotic sustained Ca^{2+} elevations, thereby preventing mitochondrial outer-membrane permeabilization [40,43]. For more detailed information on the action of Bcl-2 and Bcl-Xl on the IP_3R, the interested reader is referred to very recent reviews on the topic [44–46].

4.2. Regulation of the phosphorylation status of Bcl-2 and IP_3R1 by Bcl-2

Bcl-2's activity has been shown to be dependent on its phosphorylation state. In cells, Bcl-2 phosphorylation is induced in response to diverse stimuli including chemotherapeutic taxanes, survival factor or protein kinase C (PKC) [47]. In addition, it has been shown that Bcl-2 is phosphorylated in a cyclin-dependent kinase (CDK) 1-dependent manner in hypericin-photosensitized HeLa cells [48]. Phosphorylation of Bcl-2 induces cell-cycle arrest in G2/M and leads to apoptotic removal. Phosphorylation occurs in the unstructured loop region between BH4 and BH3 and seems generally related to inactivation of Bcl-2, since deletion of this loop or mutation of these phosphorylated sites enhances the anti-apoptotic properties of Bcl-2 [49–53]. In cycling Jurkat cells, Bcl-2 is phosphorylated by Jun N-terminal kinases (JNK) during the G2/M cell cycle at T^{69}, S^{70} and S^{87} [54]. Mutation in Bcl-2 of these 3 amino acids to alanine (Bcl-2^{AAA}) enhanced protection against Ca^{2+}-dependent death stimuli, such as arachidonic acid and H_2O_2. In addition, overexpression of Bcl-2^{AAA} in mouse embryonic fibroblasts was more potent in reducing the ER Ca^{2+} levels and inhibiting mitochondrial Ca^{2+} uptake than overexpression of wild-type Bcl-2. This indicates that phosphorylation of Bcl-2 can inactivate its anti-apoptotic action and reverse its effects on ER Ca^{2+} dynamics. This was recently confirmed in epithelial cells, where JNK1 activation occurs through $G_{\alpha 12}$, leading to Bcl-2 phosphorylation, degradation and ultimately apoptosis [55]. Dephosphorylation of Bcl-2 is mediated by different phosphatases, including PP1, PP2A and calcineurin (also named PP2B) with which Bcl-2 seems to be able to directly interact.

Calcineurin interacts with the BH4 domain of Bcl-2 in various cell types [56,57]. Subsequently, a Ca^{2+}- and CaM-dependent interaction of calcineurin was demonstrated with both Bcl-2 and IP_3R1 in various regions of the brain [58]. Moreover, as Bcl-2 seems to be required for the calcineurin-IP_3R1 interaction, it was proposed that Bcl-2 acts as a docking protein for calcineurin on IP_3R1 [59,60]. Calcineurin could then dephosphorylate both Bcl-2 and IP_3R1 and so contribute to Bcl-2's anti-apoptotic functions [59].

A Bcl-2-dependent interaction of calcineurin with the IP_3R may help resolve the long standing problem how calcineurin targets the IP_3R. Indeed, the original claim that calcineurin regulates IICR after being targeted to the IP_3R1 by FK506-binding protein (FKBP) 12 [61,62] is in contradiction with subsequent results obtained by various other groups [63-67]. Potential explanations for the effects of calcineurin on IICR have already been presented elsewhere [68]. Efficient dephosphorylation of the IP_3R by calcineurin might however also occur if the latter is targeted to the IP_3R by another docking protein as e.g. Bcl-2.

Bcl-2 has also been shown to directly interact with PP1 through a RVXF motif present in the BH1 domain of Bcl-2 (a.a. 146–150) [69]. This study provided evidence that Bcl-2 can bind through PP1 to IP_3Rs, since siRNA-mediated knockdown of PP1 reduced the interaction between Bcl-2 and IP_3R1. Moreover, the authors suggested that IP_3R1 and Bcl-2 competed for PP1 and that titrating Bcl-2 away by Bad overexpression may increase the availability of PP1 for IP_3R1 and may induce increased IICR and apoptosis. This mechanism allows for an indirect effect of Bcl-2 on IICR but would however imply that dephosphorylation of IP_3Rs activates the channel, whereas IP_3R channels are in most cases activated by phosphorylation (see part 5 and following). This interesting possibility for additional regulation should therefore be further investigated.

Recently, Bcl-2 was shown to also co-immunoprecipitate with PP2A from ER membranes [70]. Dephosphorylation of Bcl-2 apparently regulates Bcl-2 levels in a dynamic way: inhibition of PP2A led to degradation of phosphorylated Bcl-2 and a decrease in total Bcl-2 levels, whereas an increase in PP2A levels caused stabilization of endogenous Bcl-2 levels. Hence, PP2A-mediated dephosphorylation can protect Bcl-2 from proteasome-dependent degradation and therefore modulate cellular sensitivity towards ER-stress stimuli.

Finally, another study demonstrated that in the absence of Bax/Bak (i) Bcl-2 binding to IP_3R1 was strongly enhanced, and (ii) IP_3R1 was hyperphosphorylated [71]. At least part of the hyperphosphorylation was due to phosphorylation of S^{1755}, a site that can be used by either protein kinase A (PKA) or protein kinase G (PKG) (see parts 5 and 6). At the functional level, this hyperphosphorylation correlated with an increased rate of Ca^{2+} leak from the ER and a lower steady-state $[Ca^{2+}]_{ER}$. This effect could be abolished by siRNA-mediated silencing of either Bcl-2 or IP_3R1, but not of IP_3R3, indicating a specific effect of Bcl-2 on IP_3R1 [71].

Taken together these results suggest that the ratio of pro- and anti-apoptotic Bcl-2-family members specifically determines the phosphorylation status of IP_3R1. Although Bcl-2 can bind different types of phosphatases, no conclusive mechanism can be proposed to explain how this effect is mediated.

5. Regulation of the IP_3R by protein kinase A

The concept that the IP_3R can be regulated by PKA is extremely appealing, as it provides a possibility for cross-talk between the two main intracellular messengers, cAMP and Ca^{2+}. Differences in the levels of both messengers and in the intracellular densities of IP_3Rs and PKA could in this way allow for the initiation of specific Ca^{2+} signals [72]. A specific example of such a regulation can be found in the brain where the distribution and subcellular localization of phosphorylated versus unphosphorylated IP_3R1 vary markedly between brain regions and depend on the physiological condition [73].

In line with this, PKA-mediated phosphorylation of IP_3R1 appears very robust. In fact, this phosphorylation event was already demonstrated in cerebellum before the identification of the phosphoprotein as the IP_3R [74-78]. In spite of this early detection, the exact functional consequence of this phosphorylation remained for a long time controversial. This controversy may be due to the fact that multiple proteins directly or indirectly related to Ca^{2+} handling may also be the target of phosphorylation by PKA. Alternatively, it may be due to the fact that PKA-mediated phosphorylation itself is under regulatory control. Such regulation may involve a preliminary phosphorylation

by another kinase as was proposed for platelets. In those cells it appeared that the PKA-mediated inhibition of IICR only occurred when IP_3R1 was already phosphorylated by a yet unidentified endogenous kinase [79]. Also regulation by ATP can be involved: the peripheral IP_3R1 isoform contains an additional nucleotide-binding fold which seems to be unrelated to the ATP-dependent regulation of the IP_3R1 [80]. A mutation inside this fold ($G^{1690}A$) however precluded both the PKA-dependent phosphorylation of the receptor and the subsequent potentiation of the IICR, suggesting a relation between ATP binding and PKA-mediated sensitization of IP_3R1.

PKA can phosphorylate two distinct sites on IP_3R1 (S^{1588} and S^{1755}, see Fig. 1), both located in the regulatory region of the receptor and separated by the S2 splice domain that is typically present in the adult neuronal IP_3R1 isoform [81]. In this isoform, the primary phosphorylation site appears to be S^{1755}. Splicing out of the insert affects the phosphorylation process as the peripheral IP_3R isoform appears about five-fold more sensitive to PKA and is predominantly phosphorylated at S^{1588} [82]. Targeting of PKA to both the neuronal and the peripheral IP_3R1 isoforms is mediated by the anchor protein AKAP9 (also named yotiao) which interacts with a non-canonical leucine/isoleucine zipper domain in the regulatory region of the IP_3R1 (a.a. 1251–1287, see Fig. 1) [31]. In chromaffin cells, the epidermal growth factor receptor forms also part of the signaling complex, which would be recruited after stimulation by bradykinin [83].

Although it was originally proposed that the IP_3R was inhibited after phosphorylation by PKA, model systems relying on immunopurified IP_3R1 reconstituted in lipid vesicles [84] or single-channel measurements in planar lipid bilayers [30] conclusively demonstrated that PKA-mediated phosphorylation leads to a direct increase in the sensitivity of IP_3R1 towards IP_3 without shifting its Ca^{2+} sensitivity.

Similar conclusions were drawn from analysis of Ca^{2+} signals in IP_3R DT-40 triple knock-out cells heterologously expressing IP_3R1. Mutation analysis of the neuronal and peripheral isoforms of IP_3R1 indicated that phosphorylation of S^{1755} was crucial for increasing the sensitivity of the neuronal isoform while both S^{1589} and S^{1755} had to be phosphorylated to increase the sensitivity of the peripheral isoform [85,86]. Phosphomimetic mutations in IP_3Rs expressed in DT-40 cells moreover indicate that PKA-mediated phosphorylation lowers the threshold for Ca^{2+} oscillations, but does not affect their amplitude or frequency [86]. A detailed electrophysiological analysis of the IP_3R1 (peripheral isoform) in the same cell type indicated that the main effect of PKA-mediated phosphorylation was to decrease the probability of the IP_3R1 to reside in the closed state and so to increase the likelihood of extending burst activity and thus Ca^{2+} release [87].

PKA-mediated phosphorylation and activation of IP_3R1 is counteracted by PP1α [30]. Interestingly, the C-terminus of IP_3R1 can bind PP1α but not the β and γ isoforms and none of the PP1 isoforms shows significant binding to the C-termini of IP_3R2 and -3, indicating a very specific interaction [30]. As IP_3R1 can also bind PP1 indirectly via AKAP9 [31] or via associated proteins as IRBIT or Bcl-2 (see parts 3 and 4 resp., Fig. 1) it remains to be clarified which PP1-binding site(s) is (are) functional in vivo.

PKA-mediated phosphorylation cannot only affect IICR in a direct way, but might also indirectly affect the IP_3R by modulating its interaction with other regulatory factors. At least for the peripheral IP_3R1 isoform, PKA-mediated phosphorylation attenuates CaM binding to it [88]. This effect was related to the phosphorylation of the upstream PKA site and counteracted by PP1 [89]. The decreased binding of CaM may help to explain the increase in IICR observed after PKA-mediated phosphorylation. In addition, it might explain why in some other studies no PKA-mediated increase in IICR was observed, as depending of the cell type and the technique used, different levels of CaM may be present.

The potentiating effect of PKA on IICR was also observed in studies on tissues or cell types in which IP_3R1 is not the main isoform (e.g. in hepatocytes), though the presence of homomeric or heterotetrameric IP_3R1 in those cells does not allow to make conclusions on the effects of PKA on the other isoforms. As the above-mentioned residues of IP_3R1 phosphorylated by PKA are not conserved between the isoforms, differences in action of PKA can be expected. It also appears that although the leucine/isoleucine zipper region is conserved in IP_3R2 and -3, AKAP9 failed to bind to these isoforms [31].

Comparison of the three immunoprecipitated isoforms already indicated that phosphorylation was much less effective for IP_3R2 and -3 than for IP_3R1 [90]. Effects of PKA-mediated phosphorylation on specifically the IP_3R2 and -3 isoforms were therefore only investigated in a limited number of studies.

For IP_3R2 in parotid cells, evidence was presented for its PKA-mediated phosphorylation, which correlated with an increased Ca^{2+}-release activity [91]. A detailed study in the pancreatic AR4-2J cell line that expresses for 86% IP_3R2 came to the same conclusions [92] suggesting that IP_3R2 is phosphorylated and activated by PKA.

For IP_3R3, like for IP_3R1, contradictory results were published. At the one hand a PKA-mediated inhibition of IICR was demonstrated in parotid and pancreatic acinar cells [93–95]. In RINm5F insulinoma cells expressing high levels of IP_3R3 however a PKA-mediated activation of IICR was observed by different groups [90,96,97]. Three PKA-dependent phosphorylation sites were identified in IP_3R3, i.e. S^{916}, S^{934}, and S^{1832}, whereby S^{934} was the preferential phosphorylation site [98]. The relation between phosphorylation of these serine residues and changes in IP_3R3 activity is however not clear. In DT-40 cells PKA inhibited IICR after either B-cell-receptor (BCR) stimulation or activation of the protease receptor PAR2, irrespectively whether wild-type IP_3R3 or IP_3R3 mutated at one or several of the above-mentioned serine residues were expressed [99]. This observation indicates that the phosphorylated serine residues may not directly affect IP_3R3-channel function but may contribute to the scaffolding role of IP_3Rs and/or that another PKA substrate is involved in the inhibitory effect on IICR, and this in a cell-type dependent way.

6. Regulation of the IP_3R by protein kinase G

PKG has a high homology to PKA but a much more restricted tissue distribution, with highest level in the lung, cerebellum and smooth muscle [100]. In the latter two tissues it was demonstrated that IP_3R1 could be phosphorylated by PKG [101-103]. The phosphorylation event is however less pronounced than with PKA and was initially missed. PKG phosphorylated the same sites on IP_3R1 as PKA (Fig. 1) [85,101,104], though the site preferentially used seems not only to be dependent on the splice isoform but also on the phosphorylation conditions [105].

In smooth muscle, IP_3R1 and PKG are found in a multiprotein complex also containing a protein called IRAG for "IP_3R-associated cGMP kinase substrate" [106]. The latter is a relatively large protein (125 kDa) that links IP_3R1 to specifically the Iβ isoform of PKG. The formation of this complex does not depend on the phosphorylation of IRAG but when itself phosphorylated on S^{696}, IRAG leads to diminished IICR [107].

Similarly to PKA, both stimulatory [108] and inhibitory actions [109,110] on IICR were described. This might be related to the presence or absence of IRAG [107]. Another complication for the interpretation of the results is that, at least under some conditions, cAMP can lead to PKG-mediated phosphorylation [103,104], while cGMP can also induce an IP_3R-independent Ca^{2+} release [111].

Concerning the other IP_3R isoforms, much less is known. A modest phosphorylation by PKG was observed for IP_3R3, at the same site (S^{934}) that is predominantly used by PKA for this isoform [98].

7. Regulation of the IP_3R by Ca^{2+}/CaM-dependent protein kinase II

CaMKII belongs to a different type of kinase, and exists as an assembly of 8–12 monomers which is found in most tissues, though in

neurons at a particularly high concentration [112]. As CaMKII is sensitive to Ca^{2+} and CaM and has the ability to decode Ca^{2+} oscillations [112], regulation of IICR by CaMKII would constitute an obvious feedback mechanism whereby Ca^{2+} would regulate its own release.

Ca^{2+} has since long been recognized as a basic feedback regulator of the IP_3R and of the subsequent IICR (reviewed in [3,113-116]). The regulation by Ca^{2+} is biphasic, with activation in the sub-micromolar range and an inhibition at higher Ca^{2+} concentrations. Ca^{2+} activation has been consistently found in different cell types as well as in in vitro reconstitution systems, e.g. in bilayer experiments, suggesting that the determinants of the activation are probably intrinsic features of the IP_3R. On the other hand, the inhibition is highly variable, depending on IP_3R subtype, cell type and experimental conditions [3]. This can be interpreted as a result of different types of Ca^{2+}-dependent regulation including regulation of the IP_3R via Ca^{2+}/CaM and via Ca^{2+}/CaM-dependent phosphorylation [117]. As IRBIT is also a substrate for CaMKII (see part 3) an additional mechanism involving CaMKII would be that the phosphorylation of IRBIT forms part of the negative feedback mechanism.

In many studies Ca^{2+} was found to mediate its effects via Ca^{2+}-sensor proteins and particularly via CaM and the broad family of CaM-like Ca^{2+} sensors. CaM so interacts with all three IP_3R isoforms [115]. The existence of multiple sites for CaM interaction on IP_3R1 has been documented [34,88,118–120]. Inhibitory effects of CaM on IICR have been demonstrated by various groups and under various conditions 121–124]. More recently evidence was presented that additionally one of the CaM-binding sites might lead to IP_3R stimulation [120], though this latter mechanism is the matter of some debate [125]. In addition, CaM can act through activation of the multifunctional CaMKII and phosphorylation of IP_3R1 by CaMKII was already reported early on [78,126].

Up to now, precise identification and location of CaMKII phosphorylation sites on the IP_3R have not been reported. Depending on the stringency of the definition of the consensus motif multiple potential sites are possible. The R-X-X-[S/T] motif [127] is found between 11 and 19 times, depending on the isoform [128]. Screening for a consensus site L-X-R-X-X-[S/T] shared by several types of CaM-dependent kinases [129] yields however only 1 to 3 sites on each isoform, but they are not conserved in an isoform- or species-dependent way.

The role of CaMKII-mediated phosphorylation has been implicated from functional observations using inhibitors such as KN-62 [130]. CaMKII was proposed to be involved in the control of the Ca^{2+}-dependent regulation of IICR [131–133] and in the occurrence of Ca^{2+} oscillations [134–136]. In the latter study the inhibitory effect of CaMKII on IICR could be discriminated from CaMKII effects on IP_3 3-kinase [137,138]. The effects of CaMKII were also demonstrated using more specific CaMKII peptide inhibitors [136], which is important as e.g. the CaMKII inhibitor KN-93 was found to directly inhibit IP_3R1 by binding to a CaM-binding site [139].

Co-distribution of CaMKII and IP_3R3 was reported in tissues of the gastrointestinal tract [140], but the most extensive information concerning regulation by CaMKII was obtained for IP_3R2, the predominant IP_3R isoform in cardiac ventricular myocytes [141]. CaMKIIδ_B was found to co-localize with IP_3R2 in the nuclear envelope and to interact with and phosphorylate IP_3R2 within the 1-1078 N-terminal region [141]. The phosphorylation significantly decreased the open probability of IP_3R2 in lipid bilayers and it was suggested that IP_3R2 and CaMKIIδ_B may represent a signaling complex with negative feedback on IP_3R2 function in the myocyte nuclear envelope [141,142]. Such a negative feedback resulting from inhibition of IP_3R activity by CaMKII may be the cause of the effects of CaMKII on Ca^{2+} oscillations [134], neurotransmitter release [143] and on transcription-factor translocation between cytoplasm and nucleus [144]. It is well established that neuronal activity regulates gene expression via intracellular Ca^{2+} and downstream Ca^{2+}-sensitive enzymes [145]. In this respect it is relevant that IP_3R expression as well as splice selection in cerebellum granule neurons was found to be modulated by Ca^{2+}/CaM-dependent kinases (particularly CaMKIV), thus promoting the expression of a distinct splice isoform in these cells [146].

8. Regulation of the IP_3R by protein kinase C (PKC)

PKC belongs together with PKA/PKG and protein kinase B (PKB) to the so-called ABC kinases which have a conserved kinase core under allosterical control of a regulatory moiety. Based on the properties of the latter, the PKCs are usually further divided into three subfamilies, the conventional, the novel and the atypical PKCs [147]. The conventional PKCs (α, β and γ) depend for their activity on Ca^{2+} and diacylglycerol (DAG), which both increase after cell stimulation and subsequent PLC activation. Regulation of the IP_3R by PKC would therefore constitute a potential feedback mechanism. In that respect it is interesting to note that both the G-protein coupled receptors and PLC itself are also under feedback control of PKC [148]. It should be noted that PKC activation leads to changes in the subcellular localization of IP_3Rs in various cell types, which may reflect on their function [149,150]. It is however not known whether the IP_3R itself is phosphorylated during this process. Finally, it is important to realize that the various PKC isoforms can affect Ca^{2+} signaling differently [151,152].

Purified and reconstituted neuronal IP_3R1 can be phosphorylated in vitro by brain PKC [126]. The phosphorylation site is different from the PKA phosphorylation sites but is still unidentified. The general consensus motif for PKC is [R/K]-X-[S/T]-X-[R/K] [153]. This motif can be found between 3 and 6 times, depending on the IP_3R isoform [128]. Evidence suggests that the phosphorylation of IP_3R1 by PKC is specifically counteracted by the phosphatase calcineurin [61]. Calcineurin potentially interacts with the IP_3R1 through another protein, but as stated above in part 4, the identity of the docking protein, if any, is still unknown. In addition, recent results indicate that the potential docking protein FKBP12 not only could affect IICR via calcineurin but also by inhibition of the mammalian target of rapamycin (mTOR), an S/T protein kinase related to the phosphoinositol kinases that can potentiate IICR in smooth muscle [67]. It is however not known whether mTOR acts directly on the IP_3R or whether the effect is mediated by another kinase as PKC or CDK.

Interaction of PKC with its substrates can either be direct or be mediated by a scaffold protein, the receptor for activated C kinase (RACK) 1. It is therefore possible that PKC itself forms part of a multiprotein complex with the IP_3R [18]. Interestingly, RACK1 interacts with the IP_3R (Fig. 1), but no evidence was yet presented that it played a role in the anchoring of PKC to the IP_3R [154].

Functional effects of PKC-mediated phosphorylation of the IP_3R were first demonstrated in isolated rat liver nuclei where Ca^{2+} release through the IP_3R was augmented after PKC activation [155]. When calcineurin is inhibited or when the interaction of calcineurin with IP_3R1 is disturbed by e.g. FK506 [61,156,157], PKC-mediated phosphorylation of IP_3R1 is enhanced in vivo as is IICR, suggesting that phosphorylation of the IP_3R by PKC leads to increased Ca^{2+} release.

Furthermore, PKC-mediated phosphorylation of IP_3R1 can in vitro be regulated by PKA, Ca^{2+} and CaM [158]. 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_3Rs by Ca^{2+} (see part 7).

The group of Guillemette recently investigated the role of PKC-mediated phosphorylation of IP_3R2 [159] and -3 [160]. It seems that when IP_3R2 or -3 is phosphorylated by PKC, IICR is decreased in cells expressing almost exclusively those isoforms. In this case PKC is functioning as a negative regulator of intracellular Ca^{2+} release. This difference in the effect of PKC phosphorylation on IICR between IP_3R1 and the other isoforms is not unexpected as they possess different potential phosphorylation sites [128,160] and it is still neither known

which sites are used nor which are subject to further regulatory mechanisms. At least under in vitro conditions, phosphorylation of IP_3R3 by PKC is unaffected by Ca^{2+} or CaM [158].

9. Regulation of the IP_3R by protein kinase B

PKB (also called Akt) also belongs to the family of the ABC kinases. Three highly homologous isoforms (α, β, γ) are expressed in mammalian cells, all playing crucial functions in the processes of cell proliferation and cell survival [161,162]. As it is known that high levels of Ca^{2+} release can promote apoptosis [38,44,163], it is conceivable that PKB could have pro-survival effects by suppressing IICR.

All three IP_3R isoforms have an R-X-R-X-X-[S/T] consensus site for PKB, which is located in their C-terminal tail (for IP_3R1 this is S^{2681}, see Fig. 1). PKB phosphorylates the IP_3R in vitro and in vivo at this site, but a difference in IP_3R properties could at first not be shown, although in cells expressing a non-phosphorylatable IP_3R1 mutant caspase activation was stimulated after treatment with staurosporine [164]. This result is provocative and strongly suggests that PKB regulates in some way either Ca^{2+} release itself, e.g. by affecting IP_3-independent Ca^{2+} release through the channel portion of the IP_3R [165], or else interferes with the ER to mitochondria Ca^{2+}-transfer process [164]. Interestingly, a subsequent study indicated that PKB interacted between a.a. 2431 and 2749 of the IP_3R1 (Fig. 1), confirmed the phosphorylation by PKB of S^{2681}, but also demonstrated an inhibitory effect on IICR occurring simultaneously with a reduced sensitivity to apoptosis in various cell types [166]. The latter results are also in line with a more recent study investigating Ca^{2+} homeostasis in HeLa cells [167]. The reasons for the discrepancy in the effect on IICR between the first study and the latter two is not clear, but might be related to the cell types used: the low endogenous PKB activity in chicken DT-40 B-lymphocytes [166] may have obscured the effects.

10. Regulation of the IP_3R by cell cycle-dependent protein kinases

The cell cycle is a complex process exquisitely regulated by successive phosphorylation and dephosphorylation and where various protein kinases play a role. Important kinases hereby are the various CDKs, extracellular-signal regulated kinases (ERK) and polo-like kinases (PLK) [168–170].

A well-studied cellular system is the (mammalian) oocyte where it was shown that the activity of all these kinases changes during the processes of oocyte maturation and egg activation [171–173]. Moreover, in those oocytes the capacity of releasing Ca^{2+} through the IP_3R increases during maturation, reaching an optimal activity at the time of fertilization [174]. After fertilization a single, large Ca^{2+} transient is initiated, followed by Ca^{2+} oscillations that last several hours, and that disappear at interphase in a pattern which might be related to the changes in kinase activity [175–177]. Changes in IP_3R activity do not only occur in oocytes but also in somatic cells when progressing through mitotic divisions [178]. It therefore was a legitimate question to investigate whether the IP_3R is under direct control of cell cycle-dependent protein kinases.

CDK1 (also called cdc2 for cell division cycle 2) assembles with the regulatory protein cyclin B to form the maturation-promoting factor, which is important for the start of oocyte maturation. It phosphorylates substrates at an [S/T]-P-X-[K/R] consensus motif [179]. The IP_3R1 contains two phosphorylation sites for CDK, S^{421} and T^{799}, which both can be phosphorylated in vitro and in vivo by CDK1/cyclin B (Fig. 1) [180]. S^{421} is conserved in IP_3R1 from Drosophila to human but not in IP_3R2 or -3; T^{799} on the other hand is conserved in both IP_3R1 and -3. Moreover, R^{391}, R^{441}, and R^{871}, each located in an RXL cyclin-binding motif, are essential for allowing the coupling of CDK1/cyclin B to the IP_3R1 (Fig. 1) [181]. Both cyclin A and B were also shown to interact with IP_3R3, but the binding sites were not yet identified [182]. CDK1/cyclin B-mediated phosphorylation of IP_3R1, especially at T^{799}, resulted in a 3-fold increase in IP_3-binding activity and also in an increased IICR activity [180,181].

The MAP kinases ERK1 and ERK2 are cell cycle-dependent kinases that phosphorylate an [S/T]-P motif, with P-X-[S/T]-P as optimal motif [179]. In mouse IP_3R1 there are 3 potential ERK1/2 phosphorylation sites: S^{436}, T^{945} and S^{1765}. From those only S^{436} and T^{945} are conserved between mammals and Xenopus and S^{436} is also conserved in Drosophila. None of them however are conserved in IP_3R2 or -3. In addition, the docking motif for MAP kinases, a short sequence called the D domain, is found in mouse IP_3R1 (a.a. 2078–2087, see Fig. 1), suggesting a role for IP_3R1 downstream of ERK1/2 activation. In vitro, mouse cerebellar ERK1/2 interacts with this D-domain and two of the three potential sites on IP_3R1 (S^{436} and S^{1765}, see Fig. 1) are phosphorylated by ERK2 [183]. In agreement with the fact that those phosphorylation sites are not conserved between the various IP_3R isoforms, in vitro experiments on purified IP_3R1 and -3 demonstrated that only the former could be phosphorylated by ERK2 and suggested S^{436} to be the major phosphorylation site [184].

Also in agreement with the preceding, functional effects were yet only demonstrated for ERK-mediated phosphorylation of S^{436}. Interestingly, this residue is located in the hinge (a.a. 435–437) between the two parts of the IP_3-binding core, the β-trefoil and the α domain with the armadillo repeats [4]. This critical location can explain why upon phosphorylation of S^{436} by ERK the binding of the suppressor domain to the IP_3-binding core is strengthened while IP_3 binding is decreased. A decreased IICR was hereby observed [183,185].

In oocytes, a cell model expressing predominantly IP_3R1 [186], the reactivity of IP_3R1 with the mitotic protein monoclonal 2 (MPM2) antibody recognizing a [pS/pT]-P epitope [187], correlated well with ERK activity: the MPM2 phosphorylation of the IP_3R1 increases during oocyte maturation, is maximal at MII and decreases again after fertilization [184]. Pharmacological inhibition of the upstream kinase MEK by U0126 demonstrated that ERK was responsible for this MPM2 reactivity of IP_3R1. When ERK activity was inhibited, Ca^{2+} oscillations were also impaired, indicating a stimulatory effect of ERK on IICR, which is different from the effects described in somatic cells [183,185]. However this stimulation by ERK might be indirect, e.g. by regulating the relative subcellular localization of the IP_3R1 to that of another MPM2-generating kinase [184,188].

Moreover, at early stages of maturation the MPM2 reactivity of IP_3R1 was not abolished in the presence of U0126, suggesting that another kinase is then phosphorylating the IP_3R1 at an MPM2-reactive epitope [188]. A possible candidate for this is PLK1 [189]. PLK1 phosphorylates proteins on the consensus sequence [E/D]-X-[S/T]-Φ-X-[D/E] (Φ indicates any hydrophobic a.a.) [190]. There are in IP_3R1 three serines or threonines located in such consensus sites: T^{1048}, S^{1790} and T^{2656}. The latter site is very well conserved, as well across species as across the various isoforms. In contrast herewith T^{1048} and S^{1790} is conserved from Xenopus to humans in IP_3R1 but are not conserved in IP_3R2 and -3. Both IP_3R1 and -3 are in vitro phosphorylated by PLK1 (unpublished data). More importantly, we demonstrated that PLK1 is indeed the kinase responsible for the MPM2 reactivity of the IP_3R1 in mouse oocytes in vivo [188]. These results therefore strongly suggest an important role for PLK1 in the regulation of IICR during oocyte maturation. Its mechanism of action has however still to be resolved.

11. Regulation of the IP_3R by Rho kinases

Binding of hyaluronan to the plasma-membrane protein CD44 promotes adhesion, proliferation and migration of endothelial cells and these processes are mediated by monomeric GTPases as RhoA and the subsequent activation of Rho kinase. Aortic endothelial cells express the three IP_3R isoforms but after hyaluronan binding, Rho kinase-mediated phosphorylation was predominantly observed for IP_3R1, and only to a much lesser extent for IP_3R2 and -3 [191]. Functionally an increased IP_3 binding and an increased IICR were

observed, which were related to endothelial-cell migration. The process however appears much more complicated and other pathways, including IP_3 production, tyrosine kinases and interaction with cytoskeletal proteins, may all contribute to the increased IICR.

12. Regulation of the IP_3R by tyrosine kinases

The mammalian non-receptor tyrosine kinases are divided in 10 families, of which the largest is the Src family containing 8 members [192]. At least 3 members of this family were described to phosphorylate the IP_3R, though it is not yet clear whether they all act in a similar way.

The first demonstration of phosphorylation of tyrosine residues of the IP_3R1 was obtained during T-cell activation [193]. Subsequent experiments indicated that both Src and Fyn could in vitro phosphorylate IP_3R1 in brain and in T-lymphocytes [194]. Although Fyn can probably phosphorylate more than one site on IP_3R1, most of the phosphorylation occurs at a single site, Y^{353}, located in the β-trefoil domain of the IP_3-binding core, just downstream of the S1 splice site (Fig. 1) [195]. Moreover, it is this site that is specifically phosphorylated after T-cell or B-cell stimulation, suggesting its importance during these processes.

In T-lymphocytes, the interaction of the major histocompatibility complex II loaded with antigens with the T-cell receptor (TCR) leads to a cascade of events. One of the early steps is the activation of several non-receptor tyrosine kinases, leading to phosphorylation of the TCR and activation of PLCγ1. At that moment a colocalization of IP_3R1 and activated TCR occurs [196]. This colocalization is in fact the reflection of the formation of a larger macromolecular complex, as both Fyn [194] and the scaffold protein LAT, both positive regulators of PLCγ1 [197], associate with the IP_3R. Moreover, this clustering of the IP_3R1 at the side of TCR activation does not represent a general ER reorganization, but a specific movement of IP_3R1 [197]. Whether there is any mechanistic relation between IP_3R1 phosphorylation and its redistribution is here again not yet known.

Functional experiments confirm that Fyn-mediated phosphorylation of IP_3R1 is important for T-cell activation. It leads to a 5-fold increase in affinity for IP_3 [195,197] as well as to a sensitization of the channel, even at concentrations of Ca^{2+} that are normally inhibitory [194,197], which means that IP_3R1 continues to release Ca^{2+} during the phase of declining $[IP_3]$ and of sustained $[Ca^{2+}]$ elevation associated with T-cell activation [195], allowing for continuous store-operated Ca^{2+} entry and NFAT activation.

In contrast with the more widely expressed Src and Fyn, Lyn belongs to a subfamily of Src that is expressed only in hematopoietic cells, and a deficiency in Lyn is characterized by a reduction in B-cell development and activity [192]. After crosslinking of the BCR by antigen binding, a phosphorylation cascade is initiated which begins with Lyn phosphorylating the BCR as well as other proteins. In the cascade PLCγ2 is activated and IP_3 is produced. Proteins that are phosphorylated by Lyn appear to be IP_3R1 and -2 [198]. Their phosphorylation site is not yet identified, but the interaction of Lyn with the IP_3R and the subsequent phosphorylation of the latter is mediated by a scaffold protein named BANK, which is itself also phosphorylated in the process. BANK can interact through its N-terminal domain (a.a. 1–154) to the IP_3R, while a more C-terminally located part (a.a. 367–653) is involved in its interaction with Lyn. Physiologically, BANK does not lead to an upregulation of PLCγ2 activity, but, probably by mediating IP_3R phosphorylation by Lyn, enhances Ca^{2+} signaling in a process reminiscent, but not identical, to the relation between Fyn, LAT and IP_3R in T cells.

13. Conclusion and perspectives

The importance of phosphorylation/dephosphorylation in the regulation of IICR is very much dependent on the cellular context. Many different kinases can phosphorylate the IP_3R, but IP_3R isoform-specific differences occur with respect to the presence of phosphorylation sites as well as of docking sites for the different protein kinases and phosphatases. Moreover, it became clear that the formation of multiprotein complexes, whereby regulatory proteins associating with the IP_3R are themselves both substrates for kinases and phosphatases and scaffold proteins allowing the proximity of kinases and phosphatases towards the IP_3R, is important for the localized regulation of Ca^{2+} signals.

Although most effort has been directed to identify the kinases involved, it is also increasingly evident that protein phosphatases are very much involved in such multiprotein complexes. To understand the function of IICR in defined cellular conditions and/or in subcellular microdomains it will therefore be crucial to further determine which scaffolding and docking proteins are coupling kinases and phosphatases to the different IP_3R isoforms.

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