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Role of Type 1 Inositol 1,4,5-triphosphate Receptors in Mammalian Oocytes

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ABSTRACT : The ability of oocytes to undergo normal fertilization and embryo development is acquired during oocyte maturation which is transition from the germinal vesicle stage (GV), germinal vesicle breakdown (GVBD) to metaphase of meiosis II (MII). Part of this process includes redistribution of inositol 1, 4, 5-triphosphate receptor (IP3R), a predominant Ca^{2+} channel on the endoplasmic reticulum membrane. Type 1 IP3R (IP3R1) is expressed in mouse oocytes dominantly. At GV stage, IP3R1 are arranged as a network throughout the cytoplasm with minute accumulation around the nucleus. At MII stage, IP3R1 diffuses to the entire cytoplasm in a more reticular manner, and obvious clusters of IP3R1 are observed at the cortex of the egg. This structural reorganization provides acquisition of $[Ca^{2+}]_i$ oscillatory activity during fertilization. In this review, general properties of IP3R1 in somatic cells and mammalian oocyte are introduced.

Key words : IP3R1, Oocytes, Fertilization, PLCzeta

Increase of intracellular free calcium concentration ($[Ca^{2+}]_i$) is monitored in various cellular response to stimuli (Berridge et al., 2000). $[Ca^{2+}]_i$ increases is observed in most of cellular response such as secretion and contraction, proliferation, differentiation, fertilization, development and cell death (Berridge et al., 2003). Fertilization of mammalian oocytes, one of the cellular event, is controlled by increase in $[Ca^{2+}]_i$ with oscillation pattern that persists for several hours from sperm-egg fusion (Miyazaki et al., 1993). These $[Ca^{2+}]_i$ oscillations are responsible for the initiation of fertilization event including, cortical granule exocytosis to block to polyspermy, resumption of meiosis, recruitment of maternal mRNAs and activation of embryonic genome, and further embryonic development (Ajduk et al., 2008). Most Ca^{2+}-increase during fertilization originates from intracellular calcium store via 1, 4, 5 inositol triphosphate (IP3) receptors (IP3R) on the endoplasmic reticulum membrane. IP3 is a widespread signaling molecule produced as a result of hydrolysis of phosphatidylinositol 4, 5-bisphosphate (PIP_2) by phospholipase C (PLC) (Lee et al., 2006b). Egg has reported to express all three isoforms of IP3R, but type 1 IP3R (IP3R1) is present significantly larger amount in mammalian eggs (He et al., 1999). This review is to introduce the general information of IP3R and role of IP3R in mammalian egg fertilization.

$[Ca^{2+}]_i$ OSCILLATION DURING FERTILIZATION

Fertilization is a process which is regulated by IP3-

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mediated Ca^{2+}-release from intracellular Ca^{2+}-store. In mammalian oocytes, the sperm factor (SF, now it has been as known phospholipase C zeta, PLCζ) triggers activation of phosphoinositide (PI) pathway that produces IP3 and 1, 2-diacylglycerol (DAG) by hydrolysis of PIP2. Increase intracellular IP3 concentration is in charge for mediating Ca^{2+}-release from endoplasmic reticulum (ER) via IP3 receptor (Fig. 1) (Miyazaki et al., 1993; Malcuit et al., 2005; Malcuit et al., 2006; Yoon, 2011). Microinjection of 18A10 antibody, which recognizes an epitope to the Ca^{2+} channel region in the C-terminus of IP3R1, or IP3R antagonist inhibits $[Ca^{2+}]_i$ oscillation in fertilized oocytes (Miyazaki et al., 1992). Also, adenophostin A, agonist of IP3R, or thimerosal, a thiol oxidizing agent, induced $[Ca^{2+}]_i$ oscillation and further egg activation process in mature oocytes without sperm (Fissore et al., 1992; Jellerette et al., 2000).

GENERAL STRUCTURE OF IP3R1

IP3, as an intracellular second messenger, mediating Ca^{2+} -signalling in cellular response was first reported in neutrophils (Prentki et al., 1984). Autoradiographic studies with [^{3}H] IP3 represented high densities of IP3 binding in cerebellum with 100–300 times higher than in peripheral tissues (Worley et al., 1987). The purification of IP3R was reported 260 KDa protein band by electrophoretic analysis, purified protein presented seletivity for IP3 over other inositol phosphates (Supattapone et al., 1988). Three isoforms of IP3R (type 1, type 2, and type 3) have been identified by cDNA cloning. Most cells express at least one isoform and type 1 IP3R (IP3R1) is the most widely expressed in all cell types and all developmental stages (Marks, 1997).

The three IP3R isoforms demonstrate different IP3-binding affinities and sencitivity. The overall domain structure of IP3R contains a cytoplasmic N-terminus, IP3 binding domain, regulatory or modulatory domain which has multiple regulatory sites for Ca^{2+}, calmodulin dependent protein kinase, and other regulatory protein (Fig. 2). The C-terminus is channel domain including six transmembrane

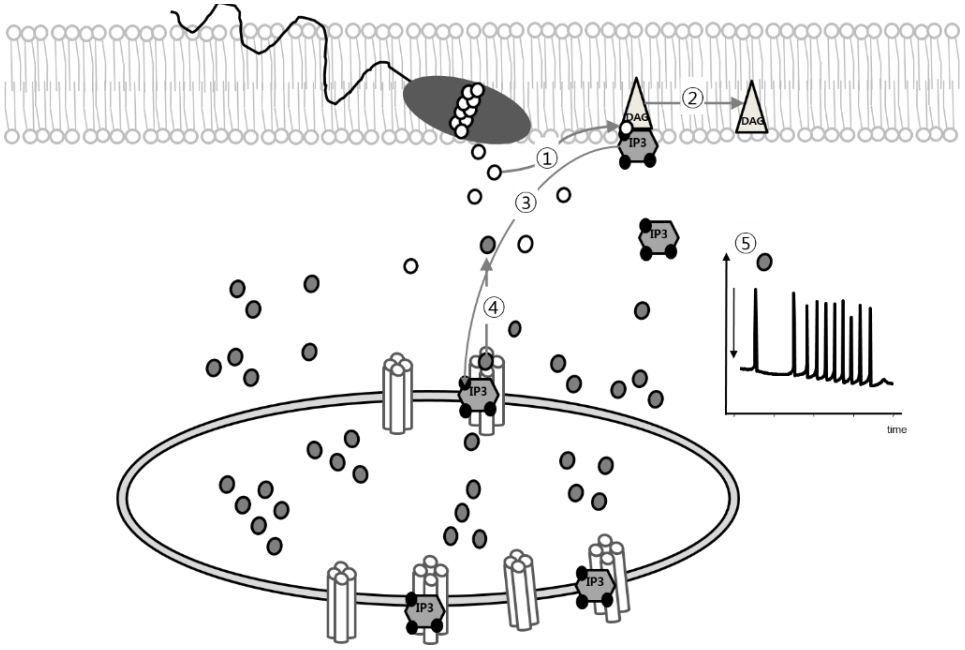

Fig. 1. Role of IP3R1 during fertilization in mammalian oocytes. ① PLCζ hydrolyzes PIP2 to DAG (③) and IP3, ② IP3 binds to IP3R1 on the endoplasmic reticulum, ④ Activated IP3R1 releases Ca^{2+} from ER to cytoplasm, ⑤ Ca^{2+} oscillation in the cytoplasm.

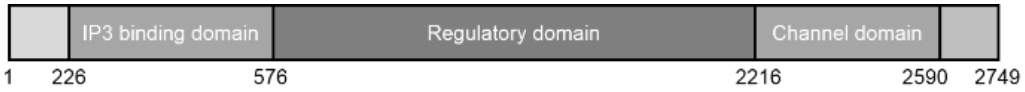

Fig. 2. Overall structure of IP3R.

domains (TMD), which form Ca^{2+}-release channels on the endoplasmic reticulum membrane (Lee et al., 2006b).

Using electron microscopy analysis, IP3R was observed tetrameric structure with reversible transition between two distinct structure, windmill and square structure (Hamada et al., 2002).

ACTIVATION OF IP3R

Ca^{2+}-release through IP3R is known to be modulated by posttranslational modification of IP3R including, binding with IP3 and Ca^{2+}, clustering of IP3R, phosphorylation / dephosphorylation, and spatial distribution in the cytoplasm.

Activation of IP3R is begun by IP3 binding to the IP3 binding domain (amino acid 226–576) and Ca^{2+} ion permeating. At least four IP3 binding sites of the tetrameric structure of IP3R are essential to activate for IP3R (Taylor & Tovey, 2010). In addition, cytosolic Ca^{2+} was shown to regulate IP3, however, the effects of Ca^{2+} were biphasic. The modest increase of intracellular Ca^{2+} induces the enhancing response to IP3, while higher increase have inhibitory effects in IP3R1 through patch clamp electrophysiology of isolated Xenopus oocyte nuclei membrane (Mak et al., 2003). At least eight Ca^{2+}-binding sites have been identified in IP3R1, Ca^{2+} promotes the transition from the square (or mushroom-like structure) to the windmill structure with relocation of four pheripheral IP3 binding domains (Hamada et al., 2003).

1. Clustering of IP3R

A commom consequence of activation of IP3R is the formation of IP3R clusters. IP3R clustering in somatic cells has been known to temporarily concur with increases in the cytosolic IP3 rathar than with $[Ca^{2+}]_i$ (Lee et al., 2006b). Green fluorecence protein-tagged IP3R1 was expressed on the rat hippocampal neuron *in vitro*, and its lateral diffusion was regulated by actin filaments and 4.1N proteins, cytoskeletal-associated proteins enriched in neuron (Fukatsu et al., 2004). Single IP3R response first, then clustered IP3Rs open togerther with local Ca^{2+}-puff, then all puffs lead to a global regenerative Ca^{2+} waves that spread out through whole cytoplasm in general somatic cells (Rahman, 2009, 2012). This IP3R clustering induced by IP3 production in the absence of a significant Ca^{2+} increase, but elevated Ca^{2+} without IP3 production did not induce IP3R clustering (Tateishi et al., 2005).

2. Phosphorylation/dephosphorylation of IP3R in general cellular response

IP3R isoforms have multiple phosphorylation consensus sites and several docking sites for protein kinase and phosphatases on their sequences. Today at least 12 different protein kinases are investigated.

1) Protein kinase A (PKA)

PKA phosphorylates two distinct sites on IP3R1 (S^{1588} and S^{1755}) in the regulatory region, and phosphorylation of this sites regulates channel open probability of IP3R1 in whole cell patch clamp study (Wagner et al., 2008). Association of IP3R1 with protein phosphatase 1 alpha facilitates dephosphorylation of PKA mediated phosphorylation (Tang et al., 2003). Also, involvement of PKA to IP3R1 activation is mediated by leucine / isoleucine zipper domain in the regulatory region (Tu et al., 2004).

2) Protein kinase G (PKG)

Another protein kinase G is shown resticted tissue distribution than PKA, could phosphorylate IP3R1 (Ser^{696}) with

IP3R-associated cGMP kinase substrate (IRAG) in microsomal smooth muscle membranes (Schlossmann et al., 2000).

3) Ca^{2+}/CaM-dependent protein kinase II

Ca^{2+}/ CaM-dependent protein kinase II (CaM KII) is a serine / threonin protein kinase expressed as an 8–12 monomers in most tissues, and highly sensitive to Ca^{2+} and calmodulin. Also it has been shown as Ca^{2+}-oscillation decoder in varioius cellular response (Dupont & Goldbeter, 1998). All three different CaM KII inhibitors (KN-93, KN-62, and Autocamtide - 2 - Related Inhibitory Peptide (AIP)) inhibited ATP-mediated $[Ca^{2+}]_i$ transient in calf pulmonary artery endothelial *in vitro* (Aromolaran & Blatter, 2005). Colocalizatioin of CaM KII and IP3R have reported in several tissues, this interaction induced phosphorylation of IP3R within N-terminal region. Besides, this phorylation of IP3R significantly decrease the open probability in lipid bilayers. It may suggest CaM KII acts on Ca^{2+} oscillations negatively (Zima et al., 2007).

4) Protein kinase C (PKC)

The actilvity of conventional PKCs, including α, β, and γ, depend on Ca^{2+} and diacylgylcerol. Also, PKC activation lead to changes of subcellular localization of IP3Rs in many cell types (Vermassen et al., 2003). Phosphorylation sites for PKC on IP3R is [R/K]-X-[S/T]-X-[R/K], and counteracts by phosphatase calcineurin (Cameron et al., 1995). In addition, there are several protein to interact with PKC for IP3R activation, FKBP12, mTOR and RACK1.

5) Protein kinase B (PKB)

All three IP3R isoforms contain an R-X-R-X-X-[S/T] consensus site for PKB in their C-terminal. PKB have a survival effects on apoptosis by inhibiting IP3-induced Ca^{2+} release on S^{2681} (Joseph & Hajnoczky, 2007).

6) Cyclin-dependent protein kinases (CDKs)

Cyclin-dependent kinases (CDKs) are a family of protein kinases and involved in cell cycle, including extracellular signal regulated kinase (ERK), and polo like kinase.

A well investigated cellular system, mammalian oocytes, was showed these protein kinases activity changes during oocyte maturation. Increase of $[Ca^{2+}]_i$ during fertilization has been reported IP3R mediated Ca^{2+} release with single, large Ca^{2+} increase followed by Ca^{2+} oscillation for several hours until pronuclear formation. These Ca^{2+} changes depend on IP3R activity through protein kinase activity. CDKs (cdc2) assemble with the regulatory protein cyclin B to form the maturation promoting factor, which is major protein for starting of oocyte maturation (Polanski et al., 2012). CDK1 phosphorylates IP3R1 at S^{421}, in IP3 binding domain and T^{799} in regulatory domain. Both sites are conserved in IP3R1 from human to Drosophila (Lee et al., 2006b). During oocyte maturation, IP3R1 undergoes cell cycle-dependent phosphorylation in mouse oocytes, M-phase kinases associates as regulators of IP3R1 in mammalian egg (Jellerette et al., 2004). CDK1/cyclin B mediated IP3R1 phosphorylation at T^{799} increases IP3 binding activity, resulting in an increase Ca^{2+}-releasing activity.

ERK1 and ERK2 are cell cycle dependent kinases and phosphorylate an P-X-[S/T]-P. In mouse IP3R1 has three ERK1/2 phosphorylation sites for ERK1/2 at S^{436}, T^{945} and S^{1765}. From in vitro phosphorylation studies represent that ERK2 phosphorylates IP3R1 at S^{436}, that mutation (S436A) abrogates IP3R1 phosphorylation (Lee et al., 2006a).

7) Tyrosine kinases

Phosphorylation of tyrosine residues of IP3R1 was observed in T-cell receptor activation, the IP3R phosphorylation is induced by tyrosine kinase, Fyn at Y^{353}. This phosphorylation was reduced in thymocytes in fyn-/- mice (Jayaraman et al., 1996). In T-cell activation, IP3R phosphorylation by Fyn induces increase of affinity for IP3 to a 5 times, which means that IP3R1 can continue to release Ca^{2+} from intracellular Ca^{2+} store during the reducing of intracellular IP3 (Cui et al., 2004).

8) Anti-apoptotic Bcl-2 protein

B-cell lymphoma 2 (Bcl-2), encoded in humans by the *Bcl2* gene, is a proapoptotic and anti-apoptotic protein with four BH domain and embedded in the endoplasmic reticulum, nuclear envelope, and mitochondrial outer membrane (Greenberg et al., 2014). Bcl-2 proteins have been associated on PKA mediated phophorylation.

CHANGES OF IP3R1 DURING OOCYTE MATURATION IN MAMMALS

Multiple changes in Ca^{2+}-response mechanism via IP3R1 including IP3R1 clustering on the plasma membrane (Mehlmann & Kline, 1994; Mehlmann et al., 1996; Machaca, 2004; Sun et al., 2011), phosphorlation of IP3R1 (Vanderheyden et al., 2009; Wakai et al., 2012; Zhang et al., 2015), have been described during oocyte maturation.

1. Type of IP3R in mammalian oocytes

As IP3R1 is observed in whole cytoplasm, 1.9 fold maturation associated increase was indicated by western blot analysis, in contrast, the type 2 and the type 3 IP3R were detect lesser in oocytes than IP3R1 (Fissore et al., 1999).

2. Mass of IP3R1 protein in oocytes

During the mouse oocyte maturation, it has known to increase an sensitivity to IP3 mediated release of intracellular calcium. 1.5 to 2 fold maturation associated increase in the mass of IP3R1 (Fissore et al., 1999) stands for this increase in IP3 sensitivity, and administrated dsRNA corresponding to the IP3R1 sequence into germinal vesicle (GV) immature oocytes and resulted in the mass of IP3R1 protein and significantly decreased Ca^{2+} transients in these oocytes than controls (Xu et al., 2003).

3. Subcellular localization, clustering and regulation of IP3R1 function in mammalian egg

The sensitivity of Ca^{2+} release has known to increase during oocyte maturation from GV stage to MII stage (Mehlmann & Kline, 1994; Mehlmann et al., 1996). In immature GV oocytes showed homogeneous distribution of IP3R1 on entire cytoplasm except geminal vesigle. However, during oocyte maturation, IP3R1 reorganized their localization and clustering itself. Most of the IP3R1 distributed in whole cytoplasm with cortical clusters near plasma membrane in large clusters, 1-2 μm in diameter (yellow arrow in Fig. 3) (Mehlmann et al., 1996). Inhibition of this clustering by MEK-specific inhibitor, U0126, reduced phosphorylation of IP3R1 and calcium release during fertilization (Lee et al., 2006a; Ito et al., 2008). Changes in IP3R1 sensitivity may underline the changes of the spatio-temporal Ca^{2+} responses during oocyte maturation. The conductivity of IP3R1 to Ca^{2+} in response to increase in IP3 is enhanced at mature MII oocytes (Machaca, 2007; Ullah et al., 2007). The Ca^{2+} transient by PLCζ in GV showed very small and narrow spike, however, that in mature MII oocytes showed big and long (4–5 mins) spike

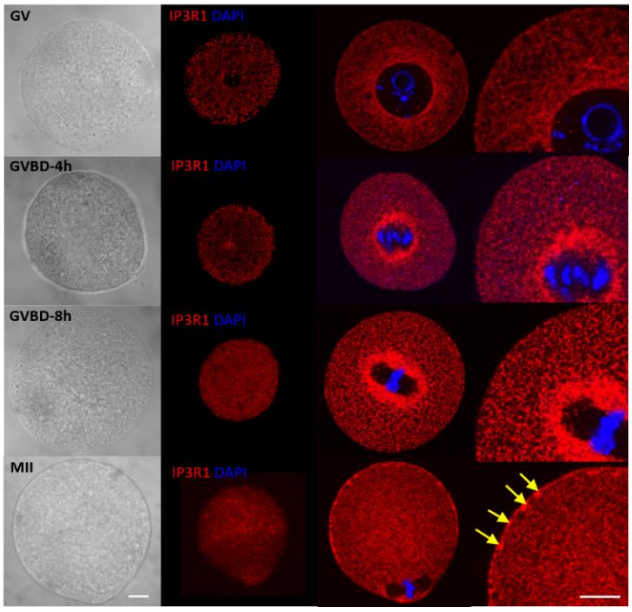

Fig. 3. IP3R1 distribution in GV, GVBD and MII mouse oocytes. GVBD oocytes were cultured for 4 hr, or 8 hr *in vitro*. Arrows indicate cortical clusters more than 1 μm in diameter. Scale bar=10 μm. GV, germinal vesicle ; GVBD, germinal vesicle breakdown.

in mouse oocytes (Machaca, 2007). Also Ca^{2+}-oscillations in response to sperm of immature oocytes were maximum three much smaller transients, which ceased after 1 hr. But the oscillation of Ca^{2+} in mature oocytes by sperm continued for 4 to 5 hrs, near pronuclear (PN) formation (Jones et al., 1995a; Jones et al., 1995b). These sensitivity of Ca^{2+} response is controlled by M phase kinase during oocyte maturation with cell cycle dependent (Jones et al., 1995a; Jellerette et al., 2004). During oocyte maturation GV immature oocytes have nonphosphorylated form of IP3R1, on the other hands, MII mature oocytes have phosphorylated IP3R1 on S^{436} by MAPK, and S^{421}, T^{799} (Lee et al., 2006b; Zhang et al., 2015).

4. IP3R1 degradation during fertilization

In mammalian oocytes, fertilization mediated Ca^{2+}-oscillations are very active at the beginning of fertilization, which is ceased as zygotes come close to the pronuclear stage. Further, more than 50% of IP3R1 mass is down-regulated by PN stage (Brind et al., 2000; Jellerette et al., 2000; Jones, 2005). These IP3R1 degradation requires continuous identical and persistantly elevated levels of IP3 by PLCζ (Jellerette et al., 2000). Also continuous degradation of the IP3R1 results in Ca^{2+}-oscillation with reduced periodicity (Lee et al., 2010). Degradation of IP3R1 is mediated by ubiquitin-proteasome pathway after IP3 binding in intact mammalian cells (Alzayady & Wojcikiewicz, 2005).

CONCLUSION

The generating of Ca^{2+}-release during fertilization provides the widespread intracellular signaling for egg activation and further embryonic development. In mammalian oocytes, Ca^{2+} oscillation during fertilization persists for several hours until the pronuclear formation. Here we interpret general charateristic of IP3R1 and the role of IP3R1 during fertilization. Further studis should be investigated the molecular mechanism that controls the activation and degradation of IP3R1 in egg activation and further embryonic development. It is hoped that this work will helpful the understanding of physiological problem in infertility or subfertility patients.

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