# Production of Intracellular Calcium Oscillation by Phospholipase C Zeta Activation in Mammalian Eggs

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**ABSTRACT** : Egg activation is a crucial step that initiates embryo development upon breaking the meiotic arrest. In mammalian, egg activation is accomplished by fusion with sperm, which induces the repeated intracellular $Ca^{2+}$- increases ($[Ca^{2+}]_i$ oscillation). Researches in mammals support the view of the $[Ca^{2+}]_i$ oscillation and egg activation is triggered by a protein factor from sperm that causes $[Ca^{2+}]_i$ release from endoplasmic reticulum, intracellular $[Ca^{2+}]_i$ store, by persistently activation of phosphoinositide pathway. It represents that the sperm factor generates production of inositol trisphosphate ($IP_3$). Recently a sperm specific form of phospholipase C zeta, referred to as PLCZ was identified. In this paper, we confer the evidence that PLCZ represent the sperm factor that induces $[Ca^{2+}]_i$ oscillation and egg activation and discuss the correlation of PLCZ and infertility.

**Key words** : Mammalian oocyte activation, Fertilization, Phospholipase C zeta

In most mammals, after luteinizing hormone surge, fully grown oocytes have progressed to the second meiotic metaphase (MII), when ovulation occurs (Schultz & Kopf, 1995). Exit from MII arrest and meiotic resumption after ovulation referred to as egg activation is achieved by fertilization. Fertilization evokes repeated increases in intracellular free calcium concentration ($[Ca^{2+}]_i$ oscillation) in the oocytes (Kline & Kline, 1992). This $[Ca^{2+}]_i$ oscillation is necessary for the completion of egg activation including cortical granule (CG) exocytosis to block polyspermy, the release of the second polar body, pronuclear formation, the expression of zygotic DNA, and initiation of mitotic division to complete meiosis. The $[Ca^{2+}]_i$ oscillations last for several hours in the oocytes of mammals, include mouse, hamster, rat, rabbit, porcine, bovine, and human. The first $[Ca^{2+}]_i$ rise is originated from sperm head penetration site on the oolemma in hamster (Miyazaki et al., 1986), and subsequent oscillations arise in the cortical region and spread in whole cytoplasm with non-wave uniform in mouse (Deguchi et al., 2000; Oda et al., 1999). The $[Ca^{2+}]_i$ oscillation at fertilization is regarded as a key regulator for modulation of the protein activity (Ducibella & Fissore, 2008; Whitaker, 2006). In this review, we introduce the relationships among $[Ca^{2+}]_i$ oscillation, egg activation, and phospholipase C zeta (PLCZ).

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## EGG ACTIVATION AND $[Ca^{2+}]_i$ OSCILLATION

After sperm and egg fusion, a factor from sperm is responsible for inducing $[Ca^{2+}]_i$ oscillation. The sperm factor (SF) triggers activation of phosphoinositide (PI) pathway which results in the production of inositol 1,4,5-triphosphate ($IP_3$) and 1,2-diacylglycerol (DAG) through the hydrolysis of phosphatidyl 4,5-bisphosphate ($PIP_2$) by a PLC (Fissore et al., 1995; Parrington et al., 1998). Increase in the intracellular $IP_3$ concentration is responsible for mediating $Ca^{2+}$- release

from endoplasmic reticulum (ER) via $IP_3$ receptor ($IP_3R$), a ligand-gated $Ca^{2+}$- channel on the ER membrane (Figure) (Malcuit et al., 2005; Malcuit et al., 2006; Miyazaki et al., 1993). $[Ca^{2+}]_i$-increase at fertilization varies widely among species. Some lower vertebrate and marine animals, such as sea urchin and frog, represent single long lasting (10 min) $[Ca^{2+}]_i$ rise (Stricker, 1999), whereas mammalian eggs show persistent and repetitive $[Ca^{2+}]_i$ oscillation for several hours. In mouse eggs, $[Ca^{2+}]_i$ oscillation by sperm persists until pronuclear formation, however in other mammalian eggs, this $[Ca^{2+}]_i$ oscillation lasts throughout the first cell cycle (Fissore & Robl, 1992; Jellerette et al., 2004; Jones et al., 1995; Marangos et al., 2003). Therefore, the differences in $[Ca^{2+}]_i$-responses among animals imply evolutionary divergence of the mechanism to induce activation of the PI pathway (Malcuit et al., 2006).

Some proteins, such as protein kinase C (PKC), have $Ca^{2+}$ binding motifs (C2), which is responsible for exocytosis in many kinds of cells, including cortical granule exocytosis in eggs (Leguia et al., 2006). Also, $Ca^{2+}$ forms a complex with EF hand proteins, such as calmodulin (CaM), which activates to PKs. $Ca^{2+}$/calmodulin dependent protein kinase II (CaM KII) has been reported as a $Ca^{2+}$ oscillation decoder in fertilization (Markoulaki et al., 2003; Yoon et al., 2011). Myosin light chain kinase (MLCK) regulates myosin II by phosphorylation on $Ser^{19}$, stimulating actin mediated ATPase activity. After fertilization, myosin II participates in cytoskeletal reorganization for CG exocytosis and cytokinesis including polar body extrusion and cleavage (Burgess, 2005; Matsumura et al., 2001). In addition, some $Ca^{2+}$-dependent phosphatases control PKs activity after fertilization (Roux et al., 2006). $[Ca^{2+}]_i$ oscillations, that continue for several

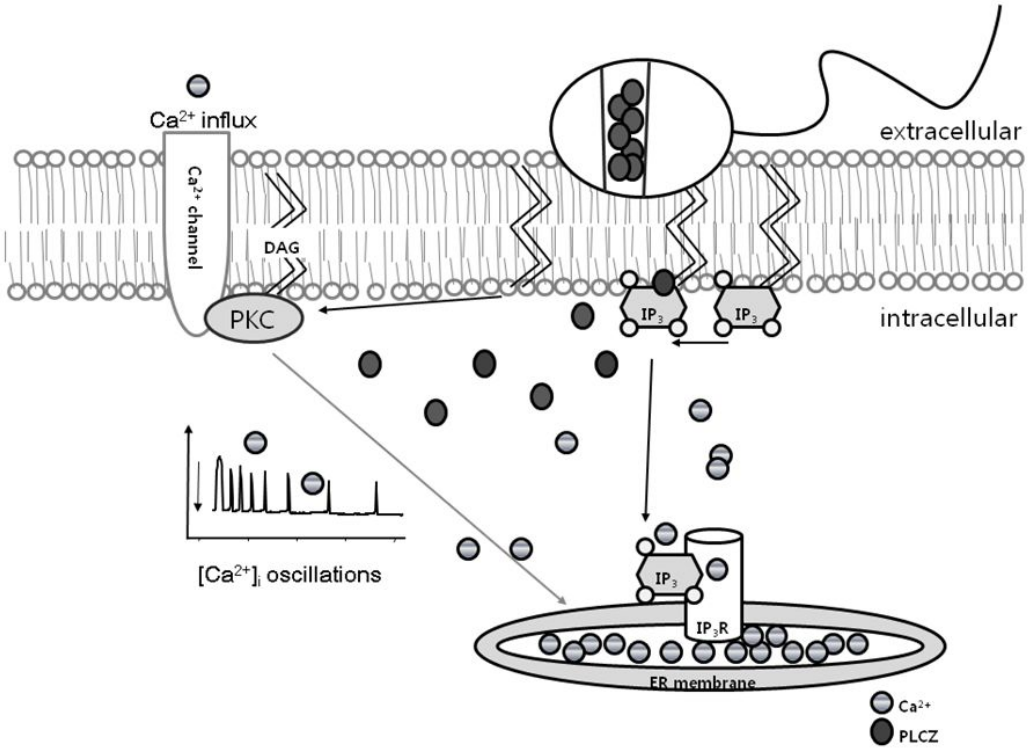


**Fig. 1. A scheme showing mechanisms which could induce $[Ca^{2+}]_i$ oscillations at fertilization in mammalian eggs.** After sperm and egg plasma membrane fusion, the sperm releases into ooplasm a soluble factor (PLCZ), which can hydrolysis $PIP_2$ into $IP_3$ and DAG. $IP_3$ binds to and activates $IP_3R$, an intracellular $Ca^{2+}$ release channel on the ER membrane. DAG may regulate intracellular $Ca^{2+}$ increase via activation of $Ca^{2+}$ channel on the plasma membrane by PKC activation. The $Ca^{2+}$-influx is necessary for refilling the ER with calcium. DAG, diacylglycerol; PKC, protein kinase C; $IP_3$, inositol 1,4,5, triphosphates; ER, endoplasmic reticulum.

hours, are also required not only the early events of egg activation and possibly but also further embryonic development to the blastocyst stage (Ducibella et al., 2002; Kline & Kline, 1992). Mouse eggs activated by exposure to cycloheximide, which inhibit protein synthesis, specially cyclin maintaining metaphase II arrest, in the condition of absence of $[Ca^{2+}]_i$ oscillations, affects embryonic development and blastocyst quality (Rogers et al., 2006).

## WHAT IS THE SPERM FACTOR MOLECULE FOR INDUCTION OF $[Ca^{2+}]_i$ OSCILLATIONS AT FERTILIZATION?

Despite several reports had been speculated the sperm factor (SF) molecules (Jones et al., 2000; Perry et al., 2000; Rice et al., 2000; Wu et al., 1997), putative properties of these molecules did not fully understand until Saunders's report (Saunders et al., 2002). Earlier studies about sperm factor reported that SF activity was released into the ooplasm rapidly (Stice & Robl, 1990; Swann, 1990), however, subsequent reports showed that at least 2 hours were required for completion of release of SF activity (Knott et al., 2003; Yoon & Fissore, 2007). Detergent- resistant sperm have $Ca^{2+}$-inducing activity at the sperm perinuclear theca area, where is involved in oocyte activation during fertilization (Fujimoto et al., 2004).

According to *in vitro* PLC assay, the SF possessed at least 100-fold higher $Ca^{2+}$-sensitivity than PLCdelta (PLC $\delta$) (Kouchi et al., 2004). Several PLC isoforms are reported in mammalian sperm (Choi et al., 2001; Fukami et al., 2001; Parrington et al., 2002). Therefore these PLC enzymes referred as candidates to be the SF. However, microinjection of these recombinant protein which expressed in sperm did not induce $[Ca^{2+}]_i$ oscillation as SF (Mehlmann et al., 2001). In a mean time, Saunders group reported a novel sperm specific PLCZ in mouse, and cRNA of PLCZ has $[Ca^{2+}]_i$ oscillation-inducing activity as SF or sperm (Saunders et al., 2002).

## NOVEL SPERM SPECIFIC PLCZ

Since PLCZ was identified in the mouse testes (Saunders et al., 2002), subsequent studies have performed, and PLCZ were cloned in human and monkey (Cox et al., 2002), porcine (Yoneda et al., 2006), rat (Ito et al., 2008; Ito et al., 2008), bovine (Ross et al., 2008), puffer fish (Coward et al., 2011), and horse (Bedford-Guaus et al., 2011). The first report of novel PLC was obtained upon examination of short EST-sequence derived from mouse and human testis, isolation, and characterization of a full-length cDNA encoding a sperm protein. The novel PLC is referred to as PLCZ (Saunders et al., 2002). PLCZ with molecular weights of approximately 70 kDa is specifically expressed in testes, in particular in spermatids, and the PLCZ is the smallest in size among PLC isoforms. Microinjection of cRNA encoding the full-length PLCZ protein into mouse eggs leads to $[Ca^{2+}]_i$ oscillation in dose dependently (Cox et al., 2002; Saunders et al., 2002). Recombinant protein of mouse PLCZ also induced $[Ca^{2+}]_i$ oscillation in mouse egg (Kouchi et al., 2004). Microinjection of SF immunodepleted with anti-PLCZ antibody failed to induce $[Ca^{2+}]_i$ oscillation in mouse egg (Fujimoto et al., 2004; Saunders et al., 2002).

As well as causing $[Ca^{2+}]_i$ oscillation, the microinjection of this protein into mature eggs leads to egg activation and embryonic development. Mouse eggs injected with PLCZ cRNA formed pronucleus, and the pronucleus are generated to diploid by cytochalacin treatment. Finally, they developed to the blastosyst stage as much as in control fertilized egg (Saunders et al., 2002). PLCZ protein localizes on equatorial/post acrosomal region of sperm head in mouse (Fujimoto et al., 2004; Yoon & Fissore, 2007), in bovine (Yoon & Fissore, 2007), hamster (Young et al., 2009) and human (Grasa et al., 2008; Yoon et al., 2008). Using different antibodies, the amount of PLCZ in a single sperm was estimated 20-50 fg or 40-50 fg (Fujimoto et al., 2004; Saunders et al., 2002). It is obvious that PLCZ has a distinct $[Ca^{2+}]_i$ oscillation activity from other PLC isoforms in egg. The PLCZ is a similar in size in all reported species (Swann et al., 2006), and the PLCZ protein did not show species specificity (Bedford-Guaus et al., 2008; Ito et al., 2008;

Ross et al., 2008). However, the isoelectirc point is various from 5.29 in rat to 9.14 in human (Swann et al., 2006), that might be the reason different enzymatic activity among different species.

The molecular structure of this protein is similar to other PLC isoforms. It consists of four EF hands domains for $Ca^{2+}$ binding, X and Y catalytic domains, and $Ca^{2+}$-dependent phospholipids binding C2 domain (Suh et al., 2008). Interestingly, PLCZ does not have the typical pleckstrin homology (PH) domain, which has been identified in all other PLC isoforms (Williams & Katan, 1996). The major role of PH domain has been known as lipid binding specificity to $PIP_2$ in PLC $\delta$1 (Paterson et al., 1995), and to heterotrimeric G protein subunit in PLC $\beta$2 and $\beta$3 (Wang et al., 2000). The four EF hand domains appear to play an important role in the enzymatic activity of PLCZ. EF1 and EF2 are important for the PLCZ activity, and EF3 is responsible for its high $Ca^{2+}$ sensitivity (Kuroda et al., 2006; Swann et al., 2006). The catalytic domain of PLCZ (X-Y linker domain) is predicted to consist of a barrel-like structure of PLCZ, and represents highly conservation in interspecies and a close homology with PLC$\delta$1 (Saunders et al., 2002). The nuclear localization signal (NLS) in the X-Y domain induces sequestration of this protein into nucleus, which may be the reason for the $[Ca^{2+}]_i$ oscillation ceases at the time of the two pronucleus formation (Larman et al., 2004; Sone et al., 2005; Stricker, 1999; Yoda et al., 2004). C2 domain in PLCZ protein has been shown to have binging activity to phospholipid-containing membrane in a $Ca^{2+}$-independent manner (Kouchi et al., 2005; Swann et al., 2006).

## PLCZ AND INFERTILITY

Assisted reproductive techniques (ART) are now in charge for up to 7% of births in some developed countries (Nasr-Esfahani et al., 2010). The advantage of intracytoplasmic sperm injection (ICSI) has overcome many male factors infertility, such as severe oligospermia, asthenospermia, teratospermia. But there are still some unexplained cases in which ICSI does not show fertilization. Only 50-70% of the eggs that undergo ICSI shows fertilization, and up to 3% of couples never achieve fertilization rate greater than 50% (Flaherty et al., 1998; Flaherty et al., 1995). Those sperm from patients who repeatedly failed ICSI were unable to induce $[Ca^{2+}]_i$ oscillations in mouse egg. Also those sperm did not represent immunoreactivity for sperm-specific PLCZ (Yoon et al., 2008). Therefore, assisted oocytes activation (AOA) is used to improve fertilization rates in the clinical laboratory. There are several reports that used AOA using, strontium chloride, $Ca^{2+}$-ionophore (or ionomycin), or electrical stimulus to improve fertilization rates and embryo quality (Nasr-Esfahani et al., 2010). Globozoospermia with deficiency of PLCZ1 could not induce $[Ca^{2+}]_i$ oscillations achieved successful fertilization by AOA with ionophore (Taylor et al., 2010). According to the proposed action of PLCZ in oocyte activation, it is possible that abnormal or reduced PLCZ expression may be a cause of fertilization failure. Silencing of PLCZ in mice suggests that reduction of this protein and the associated reduction of $[Ca^{2+}]_i$ oscillation during fertilization could lead to low developmental capacity (Knott et al., 2005). Recent studies have shown that the sperm isolated from infertile men, who failed fertilization after human ICSI, are unable to induce $[Ca^{2+}]_i$ oscillation and egg activation (Heytens et al., 2009; Yoon et al., 2008). Also, abnormal and reduced expression of PLCZ might be the reason of infertility (Yoon et al., 2008).

Although assisted reproduction techniques have been developed, there are still cases of ICSI failure with egg activation failure. In this case, Identification of PLCZ expression in sperm, using immunoblotting or immunofluorescence could be a potential and diagnostic tool in male fertility. In addition, recombinant PLCZ protein might be used in the future as a more physiological material for oocyte activation than ionophore in the clinical application. The understanding of precise mechanism of $[Ca^{2+}]_i$ oscillation by PLCZ may influence both the efficiency and the quality

of egg activation and further embryonic development.

## CONCLUSION

We are just understanding that the mechanisms of sperm induced $[Ca^{2+}]_i$ oscillation and egg activation. Here we need to continue to understanding about fertilization failure in many mammalian oocytes, including to reveal the down-stream of $[Ca^{2+}]_i$ oscillation and the reason for abnormal or reduced PLCZ protein production. Also, microinjection of recombinant PLCZ protein into mature eggs might be a more physiological oocyte activation agent instead of other chemical activation agents. Therefore, more accurate understanding of PLCZ protein will be necessary to develop the production of PLCZ protein *in vitro*, and apply in clinic and farm animal production.

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