—Review—

The role of phospholipase in sperm physiology and its therapeutic potential in male infertility

Fuminori Kimura*, Kazumi Kishida, Chisako Horikawa, Mika Izuno, Akiko Nakamura, Jun Kitazawa, Aina Morimune, Shoko Tsuji, Akie Takebayashi, Akiko Takashima, Shoji Kaku and Takashi Murakami

Department of Obstetrics and Gynecology, Shiga University of Medical Science, Shiga 520-2192, Japan

Abstract: In mammals, the role of sperm in the process of fertilization is complex, and several well-defined steps must occur for the sperm to fertilize with the oocyte. Phospholipases (PLs), which regulate the lipid composition of the sperm by hydrolyzation of the phospholipids, are involved in the regulation of the flagellar beat, capacitation, and the acrosomal reaction, as well as in the triggering of the calcium oscillations in the oocyte that lead to oocyte activation. The emerging important role of phospholipases is also revealed by the fact that alterations of sperm lipids can lead to infertility. Phospholipases, especially PLCζ, could represent therapeutic targets to overcome male infertility.

Key words: Male infertility, Fertilization, Sperm, Phospholipases

Introduction

It is well known that a proper spermatozoon is required for successful fertilization and that it is involved in the key steps of fertilization, including approach to the oocyte, penetration into the oocyte, and activation of a signal transduction cascade leading to conversion of the oocyte to a diploid embryo [1–3]. In the last decade, phospholipases have been shown to be important for these processes [2, 4, 5]. The objective of this review is to present the latest findings concerning the role of sperm phospholipases in fertility. We will briefly review the involvement of these sperm enzymes in all the key stages of fertilization and ultimately consider its therapeutic potential in oocyte activation.

Received: June 17, 2018
Accepted: August 16, 2018
*To whom correspondence should be addressed.
e-mail: kimurafu@belle.shiga-med.ac.jp

Complex Physiology and Various Abilities of Spermatozoa

Spermatozoa stored in the tail of the epididymis are still dormant, immature, and remote from their biological target [6, 7]. During their ejection from the male genital tract, they are mixed with the seminal fluid, resulting in a sudden environmental change and a physiological awakening known as the acquisition of mobility. Seminal fluid plays important and complex physiological roles [8, 9]. The acquisition of mobility allows spermatozoa to cross the cervical mucus and progress into the female genital tract [10]. Arrival in the uterine cavity and fallopian tube lead to exposure of spermatozoa to a new environment where osmolarity, pH, ionic concentrations and the composition of proteins and lipids are different. This environment supports the maturation of spermatozoa, called capacitation [11], that is required to render them competent to fertilize an oocyte. After the step of capacitation, a spermatozoon is able to fertilize. A spermatozoon must first penetrate through the egg's hard shell, known as the zona pellucida, to fuse with the oocyte. Therefore, a spermatozoon goes through a process known as the acrosome reaction [12]. This step allows secretion of proteases to facilitate passage of the spermatozoon through the zona pellucida and intervene in the fusion of the two gametes [13]. During the fusion of the two gametes, intracellular calcium levels oscillate repetitively, leading exocytosis of cortical granules released into the perivitelline space to prevent penetration of the zona pellucida (ZP) by other spermatozoa. Fusion of a spermatozoon into an oocyte initiates a complex cascade of signaling pathways in the oocyte, commencing with activation of the oocyte and eventually leading to embryogenesis in the early stages. Crucial events occurring within the fertilizing oocyte include pronuclear formation, recruitment of

maternal mRNA, release of meiosis arrest, and initiation of gene expression [14–16]. The component necessary to activate oocytes and cause these crucial events is the release of intracellular calcium (Ca^{2+}) stored in the endoplasmic reticulum (ER) [14–16]. The role of phospholipases in the spermatozoon has been shown in these critical steps for the success of fertilization.

Phospholipases

Phospholipases are enzymes that hydrolyze phospholipids into fatty acids and other lipophilic substances. The phospholipases (PLs) are classified into four major categories, PLA, PLB, PLC, and PLD [17–21], depending on the location of the enzymatic hydrolysis site. PLA1 and PLA2 hydrolyze the sn-1 bond and sn-2 bond of lysylphosphatidylglycerol (LPG), respectively. These enzymes release a fatty acid and a lysophospholipid (LP) [17]. PLBs, known as lysophospholipases, hydrolyze the two sn bonds and thus release two fatty acids [18]. PLCs specifically hydrolyze the sn-3 bonds of phosphatidylinositol 4,5-bisphosphate (PIP2), releasing an inositol 1,4,5-trisphosphate (IP3) and leaving a diacylglycerol in the membrane [20]. PLDs hydrolyze the phosphoalcoholic bond and release a phosphatidic acid and alcohol [21]. The metabolites obtained after hydrolysis act either directly as secondary messengers or by participating in the synthesis of lipid mediators (prostaglandins, leukotrienes). Each cell type possesses its own phospholipases expression profile, allowing it to respond to both external and internal stimuli [22, 23].

Several PLs have been shown to be expressed in the spermatozoa: three PLCs (PLCβ1, PLCδ4 and PLCζ), four PLA2s (cytosolic Ca^{2+}-dependent PLA2 (cPLA2), secretory Ca^{2+}-dependent PLA2 (sPLA2), Ca^{2+}-independent PLA2 (iPLA2), and platelet activating factor (PAF)-acetylhydrolase PLA2), and a PLD [24]. Their roles are different in spermatic physiology. These PLs act at different levels and regulate a variety of stages of spermatic action including spermatic mobility, capacitation, and the acrosomal reaction. PLCζ, meanwhile, has been revealed to have a pivotal role in oocyte activation at the time of fertilization.

Roles of Phospholipases in Sperm Mobility

The axoneme of the spermatozoon contains several hundred to one thousand different proteins [25]. Several enzymes are known to play pivotal roles in the flagellar beat. The serine-threonine kinase, protein kinase A (PKA), and tyrosine kinases control the cycles of phosphorylation of structural proteins of dynein [26]. Calcium, a complex secondary messenger, is also a key player in the flagellar beat. It controls soluble adenylate cyclase and therefore the production of cyclic AMP [27] and phosphorylation via calmodulin [28]. Moreover, it binds directly to the structural proteins of the axoneme and thus controls hyperactivation [29]. Although lipid signaling has been poorly studied, several studies have suggested that the membrane lipids of the flagellum are related to the flagellar beat. Asthenozoospermia has been reported to be associated with a defective lipid composition, characterized by excess cholesterol and desmosterol, a low concentration of polyunsaturated fatty acid (including docosahexaenoic acid) and an increase in saturated fatty acid [30, 31]. The presence of platelet-activating factor-acetylhydrolase PLA2 in human semen has been reported to be significantly and negatively correlated with sperm motility [31]. Lower levels of active phospho-cPLA2 in the tail and sPLA2 in the heads have been reported in asthenozoospermic patients [32, 33]. These results indicate that the lipid composition is a crucial element for a functioning flagellum and that any alteration of the enzymes involved in control of the lipid composition of the plasma membrane may cause asthenozoospermia in humans [30, 31]. However, poor spermatozoon mobility could be related to an alteration of membrane fluidity causing a different lipid composition.

Roles of Phospholipases in Capacitation and the Acrosome Reaction

Capacitation is defined as a series of complex events that affect sperm progression in the female genital tract and are necessary for sperm to fertilize an oocyte [11, 34]. This process includes biological modifications such as a change of membrane fluidity, multiple phosphorylation events, alkalization of the cytoplasm, and reorganization of lipids and membrane proteins. The role and importance of all these modifications, particularly those of the actin polymerization, in the ability of the spermatozoon to fertilize an oocyte remains poorly understood. Nevertheless, actin filament formation has been shown to be inhibited by PLD inhibitors and stimulated by exogenous PLD or phosphatidic acid [35]. This multitude of biological events is caused by sperm heterogeneity. At the end of the period of capacitation, many subpopulations of spermatozoa coexist. Some spermatozoa do not respond to stimuli of capacitation, while others react in excess (overcapacitation), leading to an acrosomal reaction that should occur later (spontaneous). In the mouse, this spontaneous acrosome reaction is partially con-

trolled by the sPLA2-GX. This PL is indeed localized in the sperm acrosome and is initially released by damaged spermatozoa. SPLA2-GX triggers an acrosome reaction in other sperm, creating a loop of amplification of the acrosomal reaction in the sperm population. Curiously, only a subpopulation of spermatozoa is sensitive to the activity of sPLA2-GX. Pharmacological inhibition or genetic deficiency of sPLA2-GX result in a decreased fertilization rate and has a deleterious effect on the development of the early embryo. However, treatment of spermatozoa with exogenous sPLA2-GX leads to the opposite effect [36]. These results suggest that appropriate lipid modifications induced by sPLA2-GX at capacitation are important for favorable fertilization. Therefore, spermatozoa are selected firstly by the crossing of the cervical mucous, then by the interactions between spermatozoa and uterotubal epithelial cells [37] and ultimately by control of the early acrosomal reaction with sPLA2-GX [38].

The roles of phospholipases in the acrosomal reaction are regulated by calcium in a manner like most of the exocytotic pathways. Calcium signaling is complex and related to a variety of cascades. In the mouse, at least three different types of channels are involved: a voltage-dependent calcium channel, receptor for IP3, and a calcium channel depending on the filling level of the calcium stocks [12]. The receptor for IP3 is a calcium channel allowing the release of calcium stored in intracellular compartments such as the acrosome. It is activated by an increase in the concentration of IP3 produced from PIP2 by PLC [39]. Although two isoforms of PLC have been characterized in the murine spermatozoon, PLCβ1, and PLCδ4, only PLCδ4 seems to intervene in the production of IP3 during the acrosomal reaction in mice. Indeed, only male mice deficient in PLCδ4 protein show decreased fertility [40]. In addition, without PLCδ4, the calcium signaling induced by ZP3 (zona protein 3), one of the natural agonists of the acrosomal reaction in the mouse, is completely inhibited [41]. It is conventionally accepted that calcium binds to the SNARE (soluble NSF attachment receptor)-synaptotagmin complex and allows fusion of the outer membrane of the acrosome with the plasma membrane [12]. However, some results suggested that PLA2 could be involved in the fusion of these two membranes via the production of lipids. Indeed, arachidonic acid and lysophosphatidylcholine are produced during the acrosomal reaction, and these two molecules are known to be produced by the hydrolysis of phospholipids with a PLA2. In addition, pretreatment of spermatozoa with a non-specific inhibitor of PLA2 blocks the acrosome reaction [24, 42].

Ca^{2+} Release Dynamics and IP3 in Oocyte during Fertilizing

To understand how the sperm initiates the Ca^{2+} signal in the oocyte, the timing and pattern of Ca^{2+} increases at fertilization need to be known. In mammals, a series of repeated spike rises in Ca^{2+}, known as Ca^{2+} oscillations, occurs as a result of release from the stock of cytoplasm [43–45], although the source of Ca^{2+} is largely via influx from outside the oocyte in some species. The first Ca^{2+} oscillations generally commences from the point of sperm infusion and continues as waves [44, 46]. In oocytes that show Ca^{2+} oscillations during fertilization, the multiple waves of Ca^{2+} stimuli change their properties over time. Mammalian eggs also exhibit multiple Ca^{2+} waves that are less clearly polarized than those of other species. The Ca^{2+} oscillations in mammalian eggs are less frequent and have large amplitudes, and they continue for several hours after sperm-oocyte fusion. The initial Ca^{2+} wave appears around the location of the sperm-oocyte fusion, spreads to the entire oocyte surface and reaches the opposite side of the spherical oocytes in 5 to 10 seconds. In the hamster, two consecutive waves, which are derived from a more diffused place away from the sperm-oocyte fusion point, follow within 5 min [47]. Continuous oscillations occur after another 5 min, when is near the time of the second Ca^{2+} wave seen in the mouse. These subsequent waves are derived from different parts of the oocyte cytoplasm during fertilization, in which they are biased towards the cortical region, and consist of very fast waves traversing around the oocytes in less than 1 second [46, 47]. The wave pattern suggests that Ca^{2+} waves originate from the region of the sperm-oocyte fusion. In other words, certain substances from the sperm or the sperm-oocyte fusion phenomena itself induce the initial Ca^{2+} wave and then induce the source of following Ca^{2+} waves in random cortical locations of the cytoplasm, spreading across the oocytes in 5–10 min. It should also be noted that Ca^{2+} oscillation in mammalian eggs occurs with lower frequency and lasts for hours. This is because long hours are needed to complete meiosis in mammals.

If certain substances from sperm are related to the Ca^{2+} release, one possible idea to explain how the sperm induce Ca^{2+} release is that sperm contain a soluble sperm factor that diffuses into the egg. This idea is underpinned by clinical procedures of intracytoplasmic sperm injection (ICSI) designed to overcome male factor infertility. When a sperm is injected into the oocyte cytoplasm, the human egg can be activated, leading to normal development [48]. Importantly, ICSI in the human

oocyte has been known to induce Ca^{2+} oscillation similar to that seen when natural fertilization occurs [49, 50]. This phenomenon is interesting because it shows that sperm-oocyte fusion itself does not need to trigger Ca^{2+} oscillations even though sperm contains a soluble peptide that can act extracellularly and induce an initial Ca^{2+} increase [51]. The important substance for Ca^{2+} release appears to be located inside the sperm head because it has been shown that the degree of sperm membrane damage required for the rapid release of sperm factors from the head is related to the determination of how soon the Ca^{2+} oscillations start [52]. Furthermore, the ICSI procedure is able to induce Ca^{2+} release in an oocyte with a sperm from a different species. Thus, a sperm factor causing Ca^{2+} oscillations is likely present.

Most cells generate Ca^{2+} by producing inositol 1,4,5-trisphosphate (IP3), which is made after enzymatic degradation of phosphatidylinositol 4,5-bisphosphate (PIP2) [53]. It is difficult to measure IP3 increases in oocytes biochemically. However, the generation of IP3 can be estimated by measuring the downregulation of IP3 receptors. In mouse eggs, the number of IP3 receptors has been known to decrease after fertilization. This decrease of IP3 receptors is measurable a few hours after the initiation of Ca^{2+} oscillations [54, 55].

IP3 injection has been reported to trigger a Ca^{2+} wave or oscillations in oocytes or eggs from a variety of mammalians [56–59]. Downregulation of the IP3 receptor can be achieved artificially by microinjecting adenophostin into immature mouse oocytes that can subsequently mature in vitro. The lack of IP3 receptors in mature eggs cause a defect in Ca^{2+} oscillations even when the eggs are fertilized with sperm. It is clear that the IP3 receptor is essential for the induction of Ca^{2+} oscillation during fertilization in mammalian eggs [60]. Inhibition of sperm-induced Ca^{2+} oscillations by a monoclonal antibody blocking the IP3 receptor has also been studied. IP3 is one of the essential signals that can induce Ca^{2+} oscillations in mammalian eggs [45]. In the mouse egg, injecting physiological amounts of IP3 induces a single large Ca^{2+} increase within a second [57, 61]. However, it is difficult to explain how stimulation with a single bolus of IP3 induces continuous low-frequency oscillations during natural fertilization. Instead, it is hypothesized that the mechanism that increase IP3 in the fertilizing oocyte may involve continuous or periodic generation of IP3. Continuous injection of IP3 generates a series of Ca^{2+} oscillations [59, 62]. Injection of the IP3 mimetic adenophostin into oocytes can induce a series of Ca^{2+} oscillations. All these results suggest the presence of a mechanism generating IP3 continuously and periodically in the oocyte during fertilization and a sperm factor producing IP3 in a way with a specific pattern of oscillations. This substance is referred to as sperm-borne oocyte activating factor (SOAF) [63].

PLCζ as the SOAF

It is generally considered that protein factors must have adequate functional and developmental properties to be considered a SOAF. Thus, a SOAF should induce Ca^{2+} oscillation from the oocyte during fertilization [1, 64, 65], and its mechanism should be accompanied by an increase in the production of IP3 regulated by the phosphoinositide signaling pathway [45]. The phospholipase C (PLC) family is comprised of enzymatic proteins in cytoplasm that catalyze the hydrolysis of PIP2 to generate IP3. IP3 induces the release of Ca^{2+} via IP3R localized on the surface of the ER [66–69] (Fig. 1A). Currently, 13 PLC isozymes are known to be categorized depending on their structure and regulatory mechanism. Several endogenous oocyte PLCs have been suggested to play a role in activation itself, but identification of sperm PLCs has become of the great interest [64, 69–71]. This is because they would become strong candidates for SOAFs. None of the identified PLC isoforms could be proved to induce Ca^{2+} release in an oocyte in a similar manner as observed during normal fertilization until 2002. At that time, the gene coding for a new PLC isoform, PLCζ, was cloned from a complementary testis DNA library of mice [72]. PLCζ is the smallest PLC known to date, and it lacks the areas usually present as the SH2 (Src homology 2), SH3 or PH (pleckstrin homology) domains. Injection of the protein or its messenger RNA into the oocyte can mimic oocyte activation and trigger calcium oscillations similar to those caused by fertilization [73]. Furthermore, microinjection of cRNA synthesized against PLCζ into mouse MII-arrested oocytes revealed a normal Ca^{2+} release profile and successful development to the blastocyst stage [64]. On the other hand, the fact that PLCζ was the sperm component responsible for Ca^{2+} release was proved by depletion of PLCζ from sperm, which resulted in the failure to generate Ca^{2+} activity. Through fractionation experiments, it was concluded that PLCζ is the only sperm protein involved in the observed Ca^{2+} oscillation [64] (Fig. 1A). PLCζ-deficient sperm, created by RNA interference technology in transgenic mice, provided further evidence showing that PLCζ is responsible for Ca^{2+} oscillation [74]. All these data suggested that PLCζ is a SOAF, although the specific receptors that interact with PLCζ have not been identified within the oocyte.

PLCζ expression is evident in three distinct localization

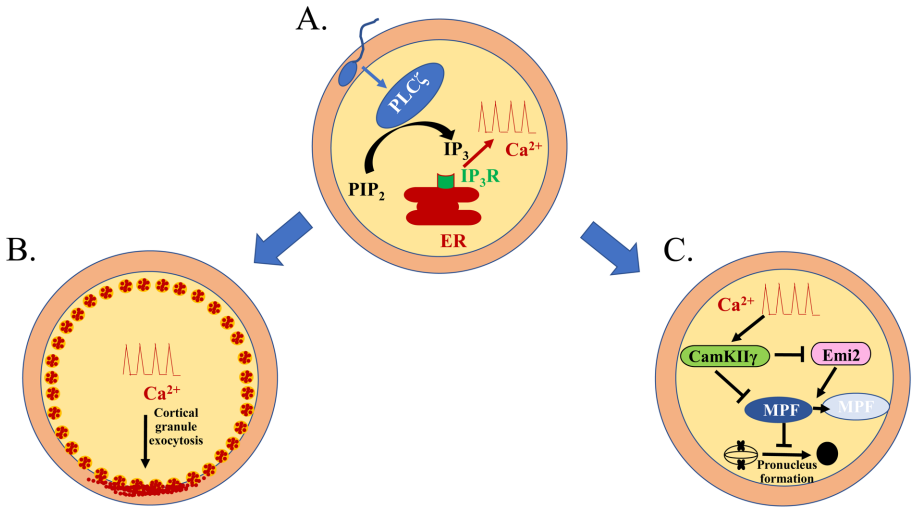

Fig. 1 A: PLCζ from the sperm produces IP3 from PIP_2 in the egg, leading to release of Ca^{2+} from the endoplasmic reticulum (ER) via IP3Rs and triggering a series of Ca^{2+} oscillations. B: Ca^{2+} oscillations release cortical granules, leading to blockage of polyspermy. C: Ca^{2+} oscillations lead to resumption of meiosis from metaphase II arrest. The resumption involves the activation of CaMKII and inactivation of Emi2, which subsequently promotes degradation of MPF. CaMKII can also inhibit MPF. Reduced levels of MPF allow reentry of the pronucleus formation. The figure is referred Sanders and Swann [99] with some modification.

patterns within the acrosomal lesion of the human sperm head, the equatorial region, and the postacrosomal region. Expression of PLCζ in different locations might suggest the possibility of different functional roles other than oocyte activation.

The first clinical evidence indicating the relevance of PLCζ in male infertility was revealed when PLCζ-deficient sperm of patients with unsuccessful results of ICSI did not induce Ca^{2+} oscillation when it was microinjected into mouse oocytes [75]. However, Ca^{2+} oscillation in oocytes was restored when PLCζ mRNA was injected with sperm, providing reliable evidence that PLCζ deficiency is associated the with infertility phenotype [75]. Defect or a relative reduction of PLCζ within sperm may explain some cases of male infertility [75–80].

Two mutations of PLCζ isoforms in an infertile nonglobozoospermic male were shown to disrupt secondary structures of the PLCζ protein, resulting in failure to produce a normal pattern of Ca^{2+} release when PLCζ H398P and PLCζ H233L cRNA, substitution of histidine for proline at position 398 (H398P) and of histidine for leucine at position 233 (H233L), were injected into mouse eggs [75, 76].

A clear relationship between PLCζ deficiency and human infertility has prompted researchers to investigate this protein for clinical application as a diagnostic biomarker as well as a therapeutic target. Indeed, multiple studies have been employed to examine the relationship of PLCζ with representative diseases and/or conditions causing male fertility by quantitatively assess PLCζ in men with globozoospermia (sperm with a large round head lacking an acrosome), low or failed fertilization, varicocele, or sperm exhibiting an altered chromatin status (DNA damage). Significant correlations between low fertilization rates and levels of PLCζ have been found with respect to such parameters, although most of these studies assessed PLCζ RNA [81–85]. Indeed, sperm PLCζ RNA levels may not entirely be reflective of PLCζ protein status in the sperm, as a role for PLCζ RNA transcripts at fertilization has yet to be elucidated [86].

Currently, fertilization failure and embryonic development failure in patients treated with ICSI are clinically treated through assisted oocyte activation (AOA), which involves the artificial induction of Ca^{2+} release. The most clinically used agent for AOA is Ca^{2+} ionophore A23187 [87, 88]. However, this Ca^{2+} ionophore is unable to induce the ideal Ca^{2+} release required for oocyte activation in humans. Thus, the clinical significance of this agent has been reported to be limited, and human oocytes are not so responsive to it in ICSI [89, 90]. This is thought to be due to the nonphysiological transient Ca^{2+} release induced within the oocyte. Ca^{2+} ionophores are able to

release all Ca^{2+} stored in the oocyte theoretically, so activation may be induced in an uncontrolled fashion [15, 88]. Furthermore, Ca^{2+} ionophores may work on multiple sites with long-term genetic/epigenetic, biochemical, and physiological effects [88, 91]. Thus, clinical treatments that can restore physiological conditions should be pursued to overcome such problems of Ca^{2+} ionophores. The usage of PLCζ protein may represent an ideal method to treat cases of oocyte activation deficiency (OAD).

Recombinant human PLCζ protein has been a goal with varying degrees of success for many laboratories in the world. Yoon *et al.* [92] achieved successful production of purified versions of human recombinant PLCζ produced in bacterial cells following an earlier unsuccessful attempt [93]. However, abnormal Ca^{2+} release profiles were observed after injection of the human recombinant PLCζ into human oocytes, and an excessively high concentration of the purified protein was needed to induce Ca^{2+} release. Nomikos *et al.* succeeded in synthesizing purified and highly active recombinant PLCζ, which induced characteristic Ca^{2+} oscillation by injection into human oocytes [94, 95]. Moreover, other groups also demonstrated that recombinant PLCζ induced Ca^{2+} oscillation and rescued failing oocyte activation in mice [96, 97]. These results strongly suggested crucial roles of PLCζ in the process of Ca^{2+} oscillation and oocyte activation.

On the other hand, the role of sperm-induced Ca^{2+} oscillation is not only to prevent polyspermy in eggs via the cortical reaction (Fig. 1B) but also to downregulate maturation-promoting factor (MPF), which is responsible for the oocyte arrest in metaphase II stage, via a signaling pathway involving calmodulin-dependent protein kinase II (CamKIIγ) and early mitotic inhibitor 2 (Emi2) [98, 99] (Fig. 1C). The decline of MPF activity leads to formation of pronuclei. MPF levels in the oocyte are able to be decreased in various ways, making it possible to trigger egg activation and development of embryos to the blastocyst stage in vitro even without Ca^{2+} oscillation [100, 101]. Furthermore, doubts have been raised about a role for PLCζ in the process of egg activation because of the absence of PLCζ in the detergent-resistant perinuclear theca fraction where a SOAF should reside and the lack of correlation between the levels and distribution of PLCζ and the success rate of fertilization.

However, recently, two groups succeeded in the generation of *Plcz1* KO mice with the CRISPR/CAS9 system and revealed the significance of PLCζ in the fertilization process, although *Plcz1* KO male mice which were generated by the classical method were defective in the spermatogenesis [102–104]. Hachem *et al.* showed that sperm were generated in Plcz1 KO mice and that the sperm from *Plcz1* KO mice failed to trigger Ca^{2+} oscillation, resulting in increase of polyspermy. However, a few eggs fertilized with the sperm from *Plcz1* KO male mice could develop and pups were born from wt female mice mated with *Plcz1* KO male mice. Thus, *Plcz1* KO male mice are subfertile but not sterile. These results suggested that even in the absence of PLCζ, egg activation can eventually occur via an alternative signal pathway [102]. Nozawa *et al.* showed similar results for the reproductive phenotype of *Plcz1* KO male mice, although they showed the presence of atypical Ca^{2+} stimuli in all oocytes in from normal fertilization [103]. These results suggested not only the significance of PLCζ in the process of Ca^{2+} oscillation and oocyte activation but also its potential as a therapeutic targets to overcome male infertility.

Conclusion

The spermatozoon is one of the most differentiated cells in mammals, and its development requires an extremely complicated process. Phospholipases, by hydrolyzing various phospholipids, have been found to be critical in sperm processes such as 1) control of flagellum beats; 2) capacitation, the molecular transformations preparing the sperm for fertilization; 3) acrosome reaction; and 4) oocyte activation by eliciting calcium oscillations. The emerging important role of phospholipases is also due to the fact that alterations of sperm lipids can lead to infertility. Phospholipases may represent valuable agents to develop anti- and/or pro-fertility agent, especially for oocyte activation to induce IP3 and Ca^{2+} oscillation [5, 80].

Conflict of Interest

The authors declare they have no conflict of interest.

Acknowledgement

None

References

1) Kashir, J., Heindryckx, B., Jones, C., De Sutter, P., Parrington, J. and Coward, K. (2010): Oocyte activation, phospholipase C zeta and human infertility. Hum. Reprod. Update, 16, 690–703. [Medline] [CrossRef]
2) Tosti, E., and Ménézo, Y. (2016): Gamete activation: basic knowledge and clinical applications. Hum. Reprod. Update, 22, 420–439. [Medline] [CrossRef]
3) Georgadaki, K., Khoury, N., Spandidos, D.A. and

Zoumpourlis, V. (2016): The molecular basis of fertilization (Review) (Review). Int. J. Mol. Med., 38, 979–986. [Medline] [CrossRef]
4) Arnoult, C., Escoffier, J., Munch, L., Pierre, V., Hennebicq, S., Lambeau, G. and Ray, P. (2012): [Do phospholipases, key enzymes in sperm physiology, represent therapeutic challenges?]. Med. Sci. (Paris), 28, 512–518. (in French) [Medline] [CrossRef]
5) Amdani, S.N., Yeste, M., Jones, C. and Coward, K. (2015): Sperm Factors and Oocyte Activation: Current Controversies and Considerations. Biol. Reprod., 93, 50. [Medline] [CrossRef]
6) Verma, R.J. (2001): Sperm quiescence in cauda epididymis: a mini-review. Asian J. Androl., 3, 181–183. [Medline]
7) Ghosh, P., Mukherjee, S., Bhoumik, A. and Dungdung, S.R. (2018): A novel epididymal quiescence factor inhibits sperm motility by modulating NOS activity and intracellular NO-cGMP pathway. J. Cell. Physiol., 233, 4345–4359. [Medline] [CrossRef]
8) Robertson, S.A. (2005): Seminal plasma and male factor signalling in the female reproductive tract. Cell Tissue Res., 322, 43–52. [Medline] [CrossRef]
9) Rodríguez-Martínez, H., Kvist, U., Ernerudh, J., Sanz, L. and Calvete, J.J. (2011): Seminal plasma proteins: what role do they play? Am. J. Reprod. Immunol., 66,(Suppl 1): 11–22. [Medline] [CrossRef]
10) Hung, P.H., and Suarez, S.S. (2010): Regulation of sperm storage and movement in the ruminant oviduct. Soc. Reprod. Fertil. Suppl., 67, 257–266. [Medline]
11) Travis, A.J., and Kopf, G.S. (2002): The role of cholesterol efflux in regulating the fertilization potential of mammalian spermatozoa. J. Clin. Invest., 110, 731–736. [Medline] [CrossRef]
12) Florman, H.M., Jungnickel, M.K. and Sutton, K.A. (2008): Regulating the acrosome reaction. Int. J. Dev. Biol., 52, 503–510. [Medline] [CrossRef]
13) Inoue, N., Ikawa, M., Isotani, A. and Okabe, M. (2005): The immunoglobulin superfamily protein Izumo is required for sperm to fuse with eggs. Nature, 434, 234–238. [Medline] [CrossRef]
14) Stricker, S.A. (1999): Comparative biology of calcium signaling during fertilization and egg activation in animals. Dev. Biol., 211, 157–176. [Medline] [CrossRef]
15) Ducibella, T., and Fissore, R. (2008): The roles of Ca2+, downstream protein kinases, and oscillatory signaling in regulating fertilization and the activation of development. Dev. Biol., 315, 257–279. [Medline] [CrossRef]
16) Kashir, J., Deguchi, R., Jones, C., Coward, K. and Stricker, S.A. (2013): Comparative biology of sperm factors and fertilization-induced calcium signals across the animal kingdom. Mol. Reprod. Dev., 80, 787–815. [Medline] [CrossRef]
17) Murakami, M., and Lambeau, G. (2013): Emerging roles of secreted phospholipase A(2) enzymes: an update. Biochimie, 95, 43–50. [Medline] [CrossRef]
18) Tojo, H., and Okamoto, M. (1999): [Phospholipase B/lipase belonging to a new lipase family]. Tanpakushitsu Kakusan Koso, 44,(Suppl): 1032–1037. (in Japanese) [Medline]
19) Xu, S., Zhao, L., Larsson, A. and Venge, P. (2009): The identification of a phospholipase B precursor in human neutrophils. FEBS J., 276, 175–186. [Medline] [CrossRef]
20) Kadamur, G., and Ross, E.M. (2013): Mammalian phospholipase C. Annu. Rev. Physiol., 75, 127–154. [Medline] [CrossRef]
21) Frohman, M.A. (2015): The phospholipase D superfamily as therapeutic targets. Trends Pharmacol. Sci., 36, 137–144. [Medline] [CrossRef]
22) Lambeau, G., and Gelb, M.H. (2008): Biochemistry and physiology of mammalian secreted phospholipases A2. Annu. Rev. Biochem., 77, 495–520. [Medline] [CrossRef]
23) Wymann, M.P., and Schneiter, R. (2008): Lipid signalling in disease. Nat. Rev. Mol. Cell Biol., 9, 162–176. [Medline] [CrossRef]
24) Roldan, E.R., and Shi, Q.X. (2007): Sperm phospholipases and acrosomal exocytosis. Front. Biosci., 12, 89–104. [Medline] [CrossRef]
25) Escalier, D. (2006): Knockout mouse models of sperm flagellum anomalies. Hum. Reprod. Update, 12, 449–461. [Medline] [CrossRef]
26) Luconi, M., Carloni, V., Marra, F., Ferruzzi, P., Forti, G. and Baldi, E. (2004): Increased phosphorylation of AKAP by inhibition of phosphatidylinositol 3-kinase enhances human sperm motility through tail recruitment of protein kinase A. J. Cell Sci., 117, 1235–1246. [Medline] [CrossRef]
27) Carlson, A.E., Hille, B. and Babcock, D.F. (2007): External Ca2+ acts upstream of adenylyl cyclase SACY in the bicarbonate signaled activation of sperm motility. Dev. Biol., 312, 183–192. [Medline] [CrossRef]
28) Marín-Briggiler, C.I., Jha, K.N., Chertihin, O., Buffone, M.G., Herr, J.C., Vazquez-Levin, M.H. and Visconti, P.E. (2005): Evidence of the presence of calcium/calmodulin-dependent protein kinase IV in human sperm and its involvement in motility regulation. J. Cell Sci., 118, 2013–2022. [Medline] [CrossRef]
29) Suarez, S.S. (2008): Control of hyperactivation in sperm. Hum. Reprod. Update, 14, 647–657. [Medline] [CrossRef]
30) Aksoy, Y., Aksoy, H., Altinkaynak, K., Aydin, H.R. and Ozkan, A. (2006): Sperm fatty acid composition in subfertile men. Prostaglandins Leukot. Essent. Fatty Acids, 75, 75–79. [Medline] [CrossRef]
31) Buffone, M.G., Verstraeten, S.V., Calamera, J.C. and Doncel, G.F. (2009): High cholesterol content and decreased membrane fluidity in human spermatozoa are associated with protein tyrosine phosphorylation and functional deficiencies. J. Androl., 30, 552–558. [Medline] [CrossRef]
32) Zhu, J., Massey, J.B., Mitchell-Leef, D., Elsner, C.W., Kort, H.I. and Roudebush, W.E. (2006): Platelet-activating factor acetylhydrolase activity affects sperm motility and serves as a decapacitation factor. Fertil. Steril., 85, 391–394. [Medline] [CrossRef]
33) Anfuso, C.D., Olivieri, M., Bellanca, S., Salmeri, M., Motta, C., Scalia, M., Satriano, C., La Vignera, S., Burrello, N., Caporarello, N., Lupo, G. and Calogero, A.E. (2015): Asthenozoospermia and membrane remodeling enzymes: a new role for phospholipase A2. Andrology, 3, 1173–1182. [Medline] [CrossRef]
34) Salicioni, A.M., Platt, M.D., Wertheimer, E.V., Arcelay, E.,

Allaire, A., Sosnik, J. and Visconti, P.E. (2007): Signalling pathways involved in sperm capacitation. Soc. Reprod. Fertil. Suppl., 65, 245–259. [Medline]

35) Cohen, G., Rubinstein, S., Gur, Y. and Breitbart, H. (2004): Crosstalk between protein kinase A and C regulates phospholipase D and F-actin formation during sperm capacitation. Dev. Biol., 267, 230–241. [Medline] [CrossRef]

36) Escoffier, J., Jemel, I., Tanemoto, A., Taketomi, Y., Payre, C., Coatrieux, C., Sato, H., Yamamoto, K., Masuda, S., Pernet-Gallay, K., Pierre, V., Hara, S., Murakami, M., De Waard, M., Lambeau, G. and Arnoult, C. (2010): Group X phospholipase A2 is released during sperm acrosome reaction and controls fertility outcome in mice. J. Clin. Invest., 120, 1415–1428. [Medline] [CrossRef]

37) Holt, W.V., and Fazeli, A. (2010): The oviduct as a complex mediator of mammalian sperm function and selection. Mol. Reprod. Dev., 77, 934–943. [Medline] [CrossRef]

38) Escoffier, J., Pierre, V.J., Jemel, I., Munch, L., Boudhraa, Z., Ray, P.F., De Waard, M., Lambeau, G. and Arnoult, C. (2011): Group X secreted phospholipase A_2 specifically decreases sperm motility in mice. J. Cell. Physiol., 226, 2601–2609. [Medline] [CrossRef]

39) O'Toole, C.M., Arnoult, C., Darszon, A., Steinhardt, R.A. and Florman, H.M. (2000): Ca($^{2+}$) entry through store-operated channels in mouse sperm is initiated by egg ZP3 and drives the acrosome reaction. Mol. Biol. Cell, 11, 1571–1584. [Medline] [CrossRef]

40) Fukami, K., Nakao, K., Inoue, T., Kataoka, Y., Kurokawa, M., Fissore, R.A., Nakamura, K., Katsuki, M., Mikoshiba, K., Yoshida, N. and Takenawa, T. (2001): Requirement of phospholipase Cdelta4 for the zona pellucida-induced acrosome reaction. Science, 292, 920–923. [Medline] [CrossRef]

41) Fukami, K., Yoshida, M., Inoue, T., Kurokawa, M., Fissore, R.A., Yoshida, N., Mikoshiba, K. and Takenawa, T. (2003): Phospholipase Cdelta4 is required for Ca^{2+} mobilization essential for acrosome reaction in sperm. J. Cell Biol., 161, 79–88. [Medline] [CrossRef]

42) Kyono, K., Hoshi, K., Saito, A., Tsuiki, A., Hoshiai, H. and Suzuki, M. (1984): Effects of phospholipase A2, lysophosphatidyl choline, and fatty acid on the acrosome reaction of human spermatozoa. Tohoku J. Exp. Med., 144, 257–263. [Medline] [CrossRef]

43) Cuthbertson, K.S., and Cobbold, P.H. (1985): Phorbol ester and sperm activate mouse oocytes by inducing sustained oscillations in cell Ca^{2+}. Nature, 316, 541–542. [Medline] [CrossRef]

44) Dumollard, R., McDougall, A., Rouvière, C. and Sardet, C. (2004): Fertilisation calcium signals in the ascidian egg. Biol. Cell, 96, 29–36. [Medline] [CrossRef]

45) Miyazaki, S., Shirakawa, H., Nakada, K. and Honda, Y. (1993): Essential role of the inositol 1,4,5-trisphosphate receptor/Ca2+ release channel in Ca2+ waves and Ca2+ oscillations at fertilization of mammalian eggs. Dev. Biol., 158, 62–78. [Medline] [CrossRef]

46) Deguchi, R., Shirakawa, H., Oda, S., Mohri, T. and Miyazaki, S. (2000): Spatiotemporal analysis of Ca($^{2+}$) waves in relation to the sperm entry site and animal-vegetal axis during Ca($^{2+}$) oscillations in fertilized mouse eggs. Dev. Biol., 218, 299–313. [Medline] [CrossRef]

47) Miyazaki, S., Hashimoto, N., Yoshimoto, Y., Kishimoto, T., Igusa, Y. and Hiramoto, Y. (1986): Temporal and spatial dynamics of the periodic increase in intracellular free calcium at fertilization of golden hamster eggs. Dev. Biol., 118, 259–267. [Medline] [CrossRef]

48) Palermo, G., Joris, H., Devroey, P. and Van Steirteghem, A.C. (1992): Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet, 340, 17–18. [Medline] [CrossRef]

49) Ogonuki, N., Sankai, T., Yagami, K., Shikano, T., Oda, S., Miyazaki, S. and Ogura, A. (2001): Activity of a sperm-borne oocyte-activating factor in spermatozoa and spermatogenic cells from cynomolgus monkeys and its localization after oocyte activation. Biol. Reprod., 65, 351–357. [Medline] [CrossRef]

50) Tesarik, J., and Sousa, M. (1994): Comparison of Ca^{2+} responses in human oocytes fertilized by subzonal insemination and by intracytoplasmic sperm injection. Fertil. Steril., 62, 1197–1204. [Medline] [CrossRef]

51) Nakano, T., and Kyozuka, K. (2015): Soluble sperm extract specifically recapitulates the initial phase of the Ca2+ response in the fertilized oocyte of P. occelata following a G-protein/ PLCβ signaling pathway. Zygote, 23, 821–835. [Medline] [CrossRef]

52) Yanagida, K., Katayose, H., Hirata, S., Yazawa, H., Hayashi, S. and Sato, A. (2001): Influence of sperm immobilization on onset of Ca($^{2+}$) oscillations after ICSI. Hum. Reprod., 16, 148–152. [Medline] [CrossRef]

53) Berridge, M.J. (2007): Inositol trisphosphate and calcium oscillations. Biochem. Soc. Symp., 74, 1–7. [Medline] [CrossRef]

54) Malcuit, C., Knott, J.G., He, C., Wainwright, T., Parys, J.B., Robl, J.M. and Fissore, R.A. (2005): Fertilization and inositol 1,4,5-trisphosphate (IP3)-induced calcium release in type-1 inositol 1,4,5-trisphosphate receptor down-regulated bovine eggs. Biol. Reprod., 73, 2–13. [Medline] [CrossRef]

55) Malcuit, C., Kurokawa, M. and Fissore, R.A. (2006): Calcium oscillations and mammalian egg activation. J. Cell. Physiol., 206, 565–573. [Medline] [CrossRef]

56) Galione, A., Swann, K., Georgiou, P. and Whitaker, M. (1994): Regenerative and non-regenerative calcium transients in hamster eggs triggered by inositol 1,4,5-trisphosphate. J. Physiol., 480, 465–474. [Medline] [CrossRef]

57) Miyazaki, S. (1988): Inositol 1,4,5-trisphosphate-induced calcium release and guanine nucleotide-binding protein-mediated periodic calcium rises in golden hamster eggs. J. Cell Biol., 106, 345–353. [Medline] [CrossRef]

58) Swann, K. (1994): Ca^{2+} oscillations and sensitization of Ca^{2+} release in unfertilized mouse eggs injected with a sperm factor. Cell Calcium, 15, 331–339. [Medline] [CrossRef]

59) Swann, K., Igusa, Y. and Miyazaki, S. (1989): Evidence for an inhibitory effect of protein kinase C on G-protein-mediated repetitive calcium transients in hamster eggs. EMBO J., 8, 3711–3718. [Medline] [CrossRef]

60) Brind, S., Swann, K. and Carroll, J. (2000): Inositol 1,4,5-trisphosphate receptors are downregulated in mouse oocytes

in response to sperm or adenophostin A but not to increases in intracellular Ca(2+) or egg activation. Dev. Biol., 223, 251–265. [Medline] [CrossRef]
61) Kline, J.T., and Kline, D. (1994): Regulation of intracellular calcium in the mouse egg: evidence for inositol trisphosphate-induced calcium release, but not calcium-induced calcium release. Biol. Reprod., 50, 193–203. [Medline] [CrossRef]
62) Jones, K.T., and Nixon, V.L. (2000): Sperm-induced Ca($^{2+}$) oscillations in mouse oocytes and eggs can be mimicked by photolysis of caged inositol 1,4,5-trisphosphate: evidence to support a continuous low level production of inositol 1, 4,5-trisphosphate during mammalian fertilization. Dev. Biol., 225, 1–12. [Medline] [CrossRef]
63) Perry, A.C., Wakayama, T. and Yanagimachi, R. (1999): A novel trans-complementation assay suggests full mammalian oocyte activation is coordinately initiated by multiple, submembrane sperm components. Biol. Reprod., 60, 747–755. [Medline] [CrossRef]
64) Saunders, C.M., Larman, M.G., Parrington, J., Cox, L.J., Royse, J., Blayney, L.M., Swann, K. and Lai, F.A. (2002): PLC zeta: a sperm-specific trigger of Ca($^{2+}$) oscillations in eggs and embryo development. Development, 129, 3533–3544. [Medline]
65) Lee, B., Yoon, S.Y. and Fissore, R.A. (2006): Regulation of fertilization-initiated [Ca2+]i oscillations in mammalian eggs: a multi-pronged approach. Semin. Cell Dev. Biol., 17, 274–284. [Medline] [CrossRef]
66) Swann, K., and Yu, Y. (2008): The dynamics of calcium oscillations that activate mammalian eggs. Int. J. Dev. Biol., 52, 585–594. [Medline] [CrossRef]
67) Nomikos, M., Swann, K. and Lai, F.A. (2012): Starting a new life: sperm PLC-zeta mobilizes the Ca^{2+} signal that induces egg activation and embryo development: an essential phospholipase C with implications for male infertility. BioEssays, 34, 126–134. [Medline] [CrossRef]
68) Ramadan, W.M., Kashir, J., Jones, C. and Coward, K. (2012): Oocyte activation and phospholipase C zeta (PLCζ): diagnostic and therapeutic implications for assisted reproductive technology. Cell Commun. Signal., 10, 12. [Medline] [CrossRef]
69) Gresset, A., Sondek, J. and Harden, T.K. (2012): The phospholipase C isozymes and their regulation. Subcell. Biochem., 58, 61–94. [Medline] [CrossRef]
70) Aarabi, M., Balakier, H., Bashar, S., Moskovtsev, S.I., Sutovsky, P., Librach, C.L. and Oko, R. (2014): Sperm-derived WW domain-binding protein, PAWP, elicits calcium oscillations and oocyte activation in humans and mice. FASEB J., 28, 4434–4440. [Medline] [CrossRef]
71) Coward, K., Ponting, C.P., Zhang, N., Young, C., Huang, C.J., Chou, C.M., Kashir, J., Fissore, R.A. and Parrington, J. (2011): Identification and functional analysis of an ovarian form of the egg activation factor phospholipase C zeta (PLCζ) in pufferfish. Mol. Reprod. Dev., 78, 48–56. [Medline] [CrossRef]
72) Rexhaj, E., Paoloni-Giacobino, A., Rimoldi, S.F., Fuster, D.G., Anderegg, M., Somm, E., Bouillet, E., Allemann, Y., Sartori, C. and Scherrer, U. (2013): Mice generated by in vitro fertilization exhibit vascular dysfunction and shortened life span. J. Clin. Invest., 123, 5052–5060. [Medline] [CrossRef]
73) Yoon, H.J., Bae, I.H., Kim, H.J., Jang, J.M., Hur, Y.S., Kim, H.K., Yoon, S.H., Lee, W.D. and Lim, J.H. (2013): Analysis of clinical outcomes with respect to spermatozoan origin after artificial oocyte activation with a calcium ionophore. J. Assist. Reprod. Genet., 30, 1569–1575. [Medline] [CrossRef]
74) Knott, J.G., Kurokawa, M., Fissore, R.A., Schultz, R.M. and Williams, C.J. (2005): Transgenic RNA interference reveals role for mouse sperm phospholipase Czeta in triggering Ca2+ oscillations during fertilization. Biol. Reprod., 72, 992–996. [Medline] [CrossRef]
75) Yoon, S.Y., Jellerette, T., Salicioni, A.M., Lee, H.C., Yoo, M.S., Coward, K., Parrington, J., Grow, D., Cibelli, J.B., Visconti, P.E., Mager, J. and Fissore, R.A. (2008): Human sperm devoid of PLC, zeta 1 fail to induce Ca($^{2+}$) release and are unable to initiate the first step of embryo development. J. Clin. Invest., 118, 3671–3681. [Medline] [CrossRef]
76) Heytens, E., Parrington, J., Coward, K., Young, C., Lambrecht, S., Yoon, S.Y., Fissore, R.A., Hamer, R., Deane, C.M., Ruas, M., Grasa, P., Soleimani, R., Cuvelier, C.A., Gerris, J., Dhont, M., Deforce, D., Leybaert, L. and De Sutter, P. (2009): Reduced amounts and abnormal forms of phospholipase C zeta (PLCzeta) in spermatozoa from infertile men. Hum. Reprod., 24, 2417–2428. [Medline] [CrossRef]
77) Kashir, J., Heynen, A., Jones, C., Durrans, C., Craig, J., Gadea, J., Turner, K., Parrington, J. and Coward, K. (2011): Effects of cryopreservation and density-gradient washing on phospholipase C zeta concentrations in human spermatozoa. Reprod. Biomed. Online, 23, 263–267. [Medline] [CrossRef]
78) Kashir, J., Konstantinidis, M., Jones, C., Lemmon, B., Lee, H.C., Hamer, R., Heindryckx, B., Deane, C.M., De Sutter, P., Fissore, R.A., Parrington, J., Wells, D. and Coward, K. (2012): A maternally inherited autosomal point mutation in human phospholipase C zeta (PLCζ) leads to male infertility. Hum. Reprod., 27, 222–231. [Medline] [CrossRef]
79) Kashir, J., Konstantinidis, M., Jones, C., Heindryckx, B., De Sutter, P., Parrington, J., Wells, D. and Coward, K. (2012): Characterization of two heterozygous mutations of the oocyte activation factor phospholipase C zeta (PLCζ) from an infertile man by use of minisequencing of individual sperm and expression in somatic cells. Fertil. Steril., 98, 423–431. [Medline] [CrossRef]
80) Escoffier, J., Yassine, S., Lee, H.C., Martinez, G., Delaroche, J., Coutton, C., Karaouzène, T., Zouari, R., Metzler-Guillemain, C., Pernet-Gallay, K., Hennebicq, S., Ray, P.F., Fissore, R. and Arnoult, C. (2015): Subcellular localization of phospholipase Cζ in human sperm and its absence in DPY19L2-deficient sperm are consistent with its role in oocyte activation. Mol. Hum. Reprod., 21, 157–168. [Medline] [CrossRef]
81) Aghajanpour, S., Ghaedi, K., Salamian, A., Deemeh, M.R., Tavalaee, M., Moshtaghian, J., Parrington, J. and Nasr-Esfahani, M.H. (2011): Quantitative expression of phospholipase C zeta, as an index to assess fertilization potential of

a semen sample. Hum. Reprod., 26, 2950–2956. [Medline] [CrossRef]
82) Janghorban-Laricheh, E., Ghazavi-Khorasgani, N., Tavalaee, M., Zohrabi, D., Abbasi, H. and Nasr-Esfahani, M.H. (2016): An association between sperm PLCζ levels and varicocele? J. Assist. Reprod. Genet., 33, 1649–1655. [Medline] [CrossRef]
83) Javadian-Elyaderani, S., Ghaedi, K., Tavalaee, M., Rabiee, F., Deemeh, M.R. and Nasr-Esfahani, M.H. (2016): Diagnosis of genetic defects through parallel assessment of PLCζ and CAPZA3 in infertile men with history of failed oocyte activation. Iran. J. Basic Med. Sci., 19, 281–289. [Medline]
84) Kamali-Dolat Abadi, M., Tavalaee, M., Shahverdi, A. and Nasr-Esfahani, M.H. (2016): Evaluation of PLCζ and PAWP expression in globozoospermic individuals. Cell J., 18, 438–445. [Medline]
85) Tavalaee, M., Kiani-Esfahani, A. and Nasr-Esfahani, M.H. (2017): Relationship between potential sperm factors involved in oocyte activation and sperm DNA fragmentation with intra-cytoplasmic sperm injection clinical outcomes. Cell J., 18, 588–596. [Medline]
86) Kashir, J., Nomikos, M. and Lai, F.A. (2018): Phospholipase C zeta and calcium oscillations at fertilisation: The evidence, applications, and further questions. Adv. Biol. Regul., 67, 148–162. [Medline] [CrossRef]
87) Reed, P.W., and Lardy, H.A. (1972): A23187: a divalent cation ionophore. J. Biol. Chem., 247, 6970–6977. [Medline]
88) Santella, L., and Dale, B. (2015): Assisted yes, but where do we draw the line? Reprod. Biomed. Online, 31, 476–478. [Medline] [CrossRef]
89) Yamano, S., Nakagawa, K., Nakasaka, H. and Aono, T. (2000): Fertilization failure and oocyte activation. J. Med. Invest., 47, 1–8. [Medline]
90) Neri, Q.V., Lee, B., Rosenwaks, Z., Machaca, K. and Palermo, G.D. (2014): Understanding fertilization through intracytoplasmic sperm injection (ICSI). Cell Calcium, 55, 24–37. [Medline] [CrossRef]
91) Follo, M.Y., Manzoli, L., Poli, A., McCubrey, J.A. and Cocco, L. (2015): PLC and PI3K/Akt/mTOR signalling in disease and cancer. Adv. Biol. Regul., 57, 10–16. [Medline] [CrossRef]
92) Yoon, S.Y., Eum, J.H., Lee, J.E., Lee, H.C., Kim, Y.S., Han, J.E., Won, H.J., Park, S.H., Shim, S.H., Lee, W.S., Fissore, R.A., Lee, D.R. and Yoon, T.K. (2012): Recombinant human phospholipase C zeta 1 induces intracellular calcium oscillations and oocyte activation in mouse and human oocytes. Hum. Reprod., 27, 1768–1780. [Medline] [CrossRef]
93) Cooney, M.A., Malcuit, C., Cheon, B., Holland, M.K., Fissore, R.A. and D'Cruz, N.T. (2010): Species-specific differences in the activity and nuclear localization of murine and bovine phospholipase C zeta 1. Biol. Reprod., 83, 92–101. [Medline] [CrossRef]
94) Nomikos, M., Kashir, J., Swann, K. and Lai, F.A. (2013): Sperm PLCζ: from structure to Ca2+ oscillations, egg activation and therapeutic potential. FEBS Lett., 587, 3609–3616. [Medline] [CrossRef]
95) Nomikos, M., Yu, Y., Elgmati, K., Theodoridou, M., Campbell, K., Vassilakopoulou, V., Zikos, C., Livaniou, E., Amso, N., Nounesis, G., Swann, K. and Lai, F.A. (2013): Phospholipase Cζ rescues failed oocyte activation in a prototype of male factor infertility. Fertil. Steril., 99, 76–85. [Medline] [CrossRef]
96) Kashir, J., Jones, C., Lee, H.C., Rietdorf, K., Nikiforaki, D., Durrans, C., Ruas, M., Tee, S.T., Heindryckx, B., Galione, A., De Sutter, P., Fissore, R.A., Parrington, J. and Coward, K. (2011): Loss of activity mutations in phospholipase C zeta (PLCζ) abolishes calcium oscillatory ability of human recombinant protein in mouse oocytes. Hum. Reprod., 26, 3372–3387. [Medline] [CrossRef]
97) Sanusi, R., Yu, Y., Nomikos, M., Lai, F.A. and Swann, K. (2015): Rescue of failed oocyte activation after ICSI in a mouse model of male factor infertility by recombinant phospholipase Cζ. Mol. Hum. Reprod., 21, 783–791. [Medline] [CrossRef]
98) Sobinoff, A.P., Sutherland, J.M. and Mclaughlin, E.A. (2013): Intracellular signalling during female gametogenesis. Mol. Hum. Reprod., 19, 265–278. [Medline] [CrossRef]
99) Sanders, J.R., and Swann, K. (2016): Molecular triggers of egg activation at fertilization in mammals. Reproduction, 152, R41–R50. [Medline] [CrossRef]
100) Miao, Y.L., Stein, P., Jefferson, W.N., Padilla-Banks, E. and Williams, C.J. (2012): Calcium influx-mediated signaling is required for complete mouse egg activation. Proc. Natl. Acad. Sci. USA, 109, 4169–4174. [Medline] [CrossRef]
101) Suzuki, T., Yoshida, N., Suzuki, E., Okuda, E. and Perry, A.C. (2010): Full-term mouse development by abolishing Zn^{2+}-dependent metaphase II arrest without Ca^{2+} release. Development, 137, 2659–2669. [Medline] [CrossRef]
102) Hachem, A., Godwin, J., Ruas, M., Lee, H.C., Ferrer Buitrago, M., Ardestani, G., Bassett, A., Fox, S., Navarrete, F., de Sutter, P., Heindryckx, B., Fissore, R. and Parrington, J. (2017): PLCζ is the physiological trigger of the Ca^{2+} oscillations that induce embryogenesis in mammals but conception can occur in its absence. Development, 144, 2914–2924. [Medline] [CrossRef]
103) Nozawa, K., Satouh, Y., Fujimoto, T., Oji, A. and Ikawa, M. (2018): Sperm-borne phospholipase C zeta-1 ensures monospermic fertilization in mice. Sci. Rep., 8, 1315. [Medline] [CrossRef]
104) Ito, J., Parrington, J. and Fissore, R.A. (2011): PLCζ and its role as a trigger of development in vertebrates. Mol. Reprod. Dev., 78, 846–853. [Medline] [CrossRef]