Advances in Biological Regulation 67 (2018) 148–162

Contents lists available at ScienceDirect

Advances in Biological Regulation

journal homepage: www.elsevier.com/locate/jbior

Phospholipase C zeta and calcium oscillations at fertilisation: The evidence, applications, and further questions

Junaid Kashir[a,b,c], Michail Nomikos[d], F. Anthony Lai[a,d,*]

[a] College of Biomedical & Life Sciences, School of Biosciences, Cardiff University, Cardiff, UK
[b] Alfaisal University, College of Medicine, Riyadh, Saudi Arabia
[c] King Faisal Specialist Hospital & Research Center, Department of Comparative Medicine, Riyadh, Saudi Arabia
[d] College of Medicine, Member of QU Health, Qatar University, PO Box 2713, Doha, Qatar

ARTICLE INFO

Keywords:
Phospholipase C zeta (PLCzeta)
Oocyte activation
Fertilisation
Sperm
Infertility
Assisted reproductive technology

ABSTRACT

Oocyte activation is a fundamental event at mammalian fertilisation, initiated by a series of characteristic calcium (Ca^{2+}) oscillations in mammals. This characteristic pattern of Ca^{2+} release is induced in a species-specific manner by a sperm-specific enzyme termed phospholipase C zeta (PLCζ). Reduction or absence of functional PLCζ within sperm underlies male factor infertility in humans, due to mutational inactivation or abrogation of PLCζ protein expression. Underlying such clinical implications, a significant body of evidence has now been accumulated that has characterised the unique biochemical and biophysical properties of this enzyme, further aiding the unique clinical opportunities presented. Herein, we present and discuss evidence accrued over the past decade and a half that serves to support the identity of PLCζ as the mammalian sperm factor. Furthermore, we also discuss the potential novel avenues that have yet to be examined regarding PLCζ mechanism of action in both the oocyte, and the sperm. Finally, we discuss the advances that have been made regarding the clinical therapeutic and diagnostic applications of PLCζ in potentially treating male infertility as a result of oocyte activation deficiency (OAD), and also possibly more general cases of male subfertility.

1. Introduction

Globally, conservative estimates indicate that infertility affects ~15% of couples and ~7% of men. Assisted reproductive technology (ART, a suite of clinical laboratory techniques designed to treat conditions of infertility) have resulted in ~2 million children being born (Kashir et al., 2010). However, the European Society for Human Reproduction and Embryology (ESHRE) indicates that pregnancy rates per embryo transfer remain fairly low, at ~23% after frozen embryo transfer, and ~48% after oocyte donation (Calhaz-Jorge et al., 2016), suggesting that apart from genetic causative factors underlying infertility, we have yet to resolve those unknown issues relating to abortive embryogenesis and recurrent implantation failure in the clinic. Furthermore, while known genetic causes of male infertility are attributable to ~30% of infertility cases, a larger proportion, ~50%, of male factor infertility cases remain unexplained (Kashir et al., 2010; Calhaz-Jorge et al., 2016).

Recent confirmations indicate that sperm parameters in many developed countries have declined by ~60% over the past 40 years

Abbreviations: PLCζ, phospholipase C-zeta; Ca^{2+}, calcium; PIP_{20}, phosphatidylinositol 4,5-bisphosphate; $InsP_3$, inositol 1,4,5-trisphosphate; PI_3P, phosphatidylinositol 3-phosphate; PI_5P, phosphatidylinositol 5-phosphate; IVF, in vitro fertilisation; ICSI, intracytoplasmic sperm injection; ART, assisted reproductive technology; OAD, oocyte activation deficiency

* Corresponding author. College of Biomedical & Life Sciences, School of Biosciences, Cardiff University, Cardiff, UK.
E-mail addresses: kashirj@cf.ac.uk (J. Kashir), lait@cardiff.ac.uk (F.A. Lai).

http://dx.doi.org/10.1016/j.jbior.2017.10.012
Received 25 September 2017; Received in revised form 25 October 2017; Accepted 25 October 2017
Available online 27 October 2017

(Levine et al., 2017). Thus, not only is it essential that research is undertaken to further understand the complex indications underlying infertility, but it is also necessary to improve fertility treatment success, significantly aiding infertile couples (and the institutions supporting them) who currently have no other option but to resort to repeated cycles of ART, at a great emotional and financial cost. The aforementioned worrying figures indicate that coming generations may increasingly depend upon fertility treatment. Indeed, pregnancy and delivery via conventional in vitro fertilisation (IVF; co-incubation of sperm and oocytes in culture media) or intracytoplasmic sperm injection (ICSI; microinjection of single sperm into the ooplasm) remain as low as 22.4% and 23.3% respectively per cycle (Kashir et al., 2010; Ramadan et al., 2012; Amdani et al., 2016).

While IVF offers effective treatment for many infertile couples, cases exhibiting severe male infertility (accounting for 19–57% of cases) remain untreatable by such techniques (Wilkes et al., 2009). In such cases, ICSI can be implemented to varying degrees of success (Palermo et al., 1992). However, despite such an approach, up to 5% of ICSI cycles still result in failure (Yanagida et al., 2008; Nasr-Esfahani et al., 2010). Considering that approximately 52% of all IVF cycles in the UK involve ICSI (HFEA, 2014), this represents a significant problem, and ICSI failure on average would affect over 1000 couples per year in the UK alone, particularly when one considers that ICSI is increasingly being applied.

Incorrect sperm injection, expulsion of injected sperm, and failure of sperm head decondensation are all possible underlying reasons, but are not considered to substantially contribute to fertilisation failure following ICSI (Yanagida et al., 2008; Kashir et al., 2010). Currently, ICSI failure is believed to result from a deficiency in a physiological mechanism fundamental to fertilisation, termed oocyte activation (oocyte activation deficiency; OAD) which has been attributed to cause complete fertilisation failure, or abnormally low fertilisation success after ICSI, a phenomenon that can recur throughout several treatment cycles (Sousa and Tesarik, 1994; Heindryckx et al., 2008; Kashir et al., 2010).

1.1. Oocyte activation and calcium oscillations

Mammalian reproduction involves the concerted release and fusion of male and female gametes through fertilisation, and is mediated by a series of complex cellular programmes that transforms the combined oocyte and sperm, into a totipotent embryo. However, following maturation, mammalian oocytes remain arrested at metaphase of the second meiotic division (MII), following the exclusion of the first polar body, having undergone the first meiotic division within the ovary (Jones, 2005, 2007). Alleviation of this MII arrest is a pre-requisite for subsequent embryogenesis, occurring either during or immediately following gamete fusion. This alleviation, alongside a series of synchronised concurrent events (including, but not limited to, cortical granule exocytosis, prevention of polyspermy, and pronuclear development), are collectively termed ‘oocyte activation’ (Stricker, 1999; Kashir et al., 2010, 2013; Nomikos et al., 2013a; Swann and Lai, 2013).

Throughout all phyla studied thus far, fertilisation initiates elevations in the level of intracellular free calcium concentration (Ca^{2+}) within the oocyte (Stricker, 1999; Kashir et al., 2010, 2013; Nomikos et al., 2013a; Swann and Lai, 2013), although in some cases such as that of the fruit fly *Drosophila melanogaster*, activation may occur before fertilisation (Kashir et al., 2013). The eggs of some vertebrates such as echinoderms, frogs, and fish elicit a single Ca^{2+} transient at fertilisation, while mammals and several marine invertebrates elicit a series of repetitive Ca^{2+} oscillations (Stricker, 1999; Kashir et al., 2013). Remarkably, the temporal patterns of Ca^{2+} oscillations are species-specific, with unique patterns of amplitude, duration, and frequency (Miyazaki et al., 1993; Ducibella et al., 2002, 2006; Kashir et al., 2014). Regardless of the pattern, however, Ca^{2+} transients at oocyte activation are essential. Indeed, the prevention of Ca^{2+} transients by adding Ca^{2+} chelators inhibits activation and embryogenesis (Kline and Kline, 1992), while microinjection of Ca^{2+} alone triggered mouse embryonic development to the blastocyst stage (Fulton and Whittingham, 1978).

Ca^{2+} oscillations in mammalian oocytes are a direct consequence of inositol trisphosphate (IP_3)-mediated Ca^{2+} release (Parrington, 2001; Swann et al., 2006; Whitaker, 2006; Parrington et al., 2007; Saunders et al., 2007 Swann and Yu, 2008). Blocking, or reducing levels or functionality of IP_3 receptors (IP_3Rs) in mouse and hamster oocytes inhibited Ca^{2+} oscillations and oocyte activation (Miyazaki et al., 1993; Brind et al., 2000; Jellerette et al., 2000; Xu et al., 2003), while cytosolic IP_3 concentration increases during mammalian oocyte fertilisation (Miyazaki et al., 1995) further supporting the importance of IP_3-mediated Ca^{2+} release.

Mammalian oocytes are remarkably sensitive to the precise Ca^{2+} oscillation profile elicited at fertilisation (Malcuit et al., 2006; Stitzel and Seydoux, 2007). The pattern of Ca^{2+} oscillations affect early mouse embryonic protein expression profiles (Ducibella et al., 2002), while also determining blastocyst formation, compaction, transplantation success of embryos to host mothers (Swann and Ozil, 1994; Miyazaki and Ito, 2006). Indeed, varying Ca^{2+} amplitudes and frequencies resulted in differential rates of mouse oocyte cell cycle progression (Ducibella et al., 2002, 2006). Considering human zygote cell cycle progression rates following fertilisation are proposed as indicative of optimal embryogenesis (Wong et al., 2010), Ca^{2+} oscillation profiles at activation may be of significant importance for subsequent embryogenic events (Yu et al., 2008).

1.2. The mammalian sperm factor

Many theories have attempted to explain the nature of the Ca^{2+} transients underlying oocyte activation during mammalian fertilisation, but the vast majority of these models remain insufficient to explain the characteristic nature of mammalian Ca^{2+} oscillations (Kashir et al., 2014). However, significant evidence supports the ‘sperm factor’ hypothesis as the most appropriate model of mammalian oocyte activation, including a number of other marine invertebrate species. This theory proposes that the sperm contains a soluble factor, capable of triggering Ca^{2+} release from intracellular stores following diffusion into the ooplasm from the sperm (Swann, 1990). Indeed, injection of sperm cytosolic extracts into mammalian oocytes triggered a prolonged series of Ca^{2+}