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Editorial

Challenges on Mammalian Male Pronuclear Formation in ICSI Procedure

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At fertilization two terminally differentiated cells converts into a totipotent zygote that eventually form all body cell types. Fertilization activates the oocyte and in a coordinated fashion triggers the inactive sperm nucleus to transforme into a functional male pronucleus (mPN) within the egg cytoplasm. This complex process consists of several overlapping stages including: I) breakdown of nuclear envelopes and disassembly of nuclear lamina; II) decondensation of highly compacted chromatin through substitution of protamines with histones followed by recondensation; III) swelling of the mPN and its migration towards the female PN; IV) the rapid demethylation of sperm DNA during PN development, and finally V) integration of paternal and maternal genomes [1].

Intracytoplasmic sperm injection (ICSI) is an important technology of assisted reproduction, especially in male factor infertility treatment and in endangered animal species preservation. Since the first report of ICSI success in the hamster [2], the transfer of embryos produced by ICSI has given rise to live progenies in human, laboratory, and livestock animals. Apart from application of ICSI in basic research such as research on cell cycle control and mechanisms involved in sperm-induced oocyte activation, this technique has application in sperm mediated gene transfer in production of transgenic animals and in freeze-dried sperm application for which maintenance of motility is not required [3]. While in laboratory animals and humans, ICSI alone is sufficient to activate the oocytes for further embryonic development, in other species such as cattle, ewe, pig and buffalo additional parthenogenetic activation after ICSI is necessary to activate the oocytes [4]. One possibility for this could be, in part, due to inconsistent activation of oocytes because of delayed or lack of disintegration of sperm plasma membrane within oocytes [5].

In ICSI, phospholipase C zeta (PLCζ), a sperm-borne oocyte-activating factor (SOAF) that is localized in the acrosomal and post-acrosomal regions of the perinuclear theca, may not be able to penetrate through the sperm plasma membrane, resulting in a limited amount of PLCζ available for oocyte activation [6]. On the other, oocyte activation is requisite for decondensation of the sperm nucleus as a critical process in normal fertilization [7]. During late stages of spermatogenesis in mammals, most histones bound to DNA are replaced by protamines, which results in formation of supercondensed sperm chromatin. At fertilization, the chromatin must remodeled "back" from nucleoprotamine to nucleohistone state [8]. To do this the protamines must be removed from the DNA by a process in which their disulphide bonds are reduced [9]. As disulphide bonds were reduced the links are cleaved and the coiled chromatin loops unfold and enable oocyte factors to further decondense the chromatin. In this process the oocyte contents, especially glutathione, seem to be prerequisite for the reduction of disulfide bonds and male pronuclear formation [10].

Apart from routine immobilization of a spermatozoon by tail-scoring before ICSI which can facilitate exposure of oocyte cytoplasm to SOAF and the subsequent oocyte activation that in turn can improve the male pronucleus formation, there are many approaches to improve normal fertilization following ICSI such as: sperm pretreatments to disrupt the acrosomal and sperm plasma membrane using Triton-X 100, calcium ionophores , lysolecithin and freezing/thawing without a cryoprotectant [11-13]; decondensation of sperm nuclei and destruction of protamine by treatment with disulfide-reducing agents alone or in combination with neutral detergents, anionic detergents, proteases, or salts; induction of acrosome reaction using progesterone treatment [14].

There are also other points with an effect on pronuclear formation. It has been shown that the compactness of cumulus cells surrounding the oocytes during IVM seems necessary for promoting normal cytoplasmic maturation and pronuclear formation. Additionally, in some animal species, the oocyte activation after ICSI is requisite for sperm aster formation and microtubule organization with the subsequent improvement of embryo development. Synchronization of pronuclei formation following ICSI, for instance using βME during IVM, might be another approach to improve normal fertilization [15]. There are, however, some drawback using some approaches for instance disrupting sperm membranes or isolation of sperm heads from the tails using sonication or piezo-actuated ICSI system may reduce the ability of the sperm to induce oocyte activation. It has been shown that the amounts of PLCz in sperm treated by such method are significantly lower than that in whole untreated sperm [16].

Despite all efforts to improve ICSI outcomes in term of oocyte activation and male pronuclear formation and the subsequent normal fertilization, the results still are not promising and ICSI is far less efficient in majority of livestock species.

Application of the approaches mimicking normal physiological events during sperm penetration at fertilization may be more promising. Removal of the sperm plasma membrane and acrosome, simulation the repetitive pattern of Ca^{2+} oscillations, once initiated persist for several hours, through increasing the frequency of ionomycin stimulation or other Ca^{2+} inducers, promotion of sperm aster formation and microtubule organization via more appropriate oocyte activation, enhancement of cytoplasmic maturation through considering pre-IVM systems or addition of substrates or supplements to increase ooplasm GSH contents, energy supply more accessible to sperm considering the existence of relationship between energy contribution by the sperm and the male pronuclear formation and/or accompanying such approaches with optimized sperm pretreatment and oocyte activation, all are approaches that need to be further investigated.

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