Oocyte

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The efficiency of producing embryos using in vitro technologies in cattle species remains lower when compared to other mammalian species such as mice, indicating that the proportion of female gametes that fail to develop after in vitro manipulation is considerably large. Considering that the intrinsic quality of the oocyte is one of the main factors affecting embryo production, the precise identification of noninvasive markers that predict oocyte competence is of major interest.

Keywords: Oocyte ; In vitro reproductive technology ; bovine

1. Introduction

In recent years, new knowledge in the field of assisted reproductive technologies (ART, has allowed researchers and practitioners to reach new hallmarks in oocyte and sperm in vitro competence. Gamete competence is the ability to undergo successful fertilization and develop a normal blastocyst that is capable of implanting in the uterus and generate viable offspring [1]. Many researchers are focused on identifying cellular and molecular markers to select the most competent oocyte and spermatozoon to produce embryos with higher implantation potential [2].

Although it is well known that the most common applications of ARTs in livestock species are for research purposes, some techniques, particularly in vitro embryo production (IVP), have become commercially viable and are extensively used for animal breeding [3]. Nonetheless, the efficiency of IVP technologies in livestock species, such as bovine, equine, and porcine, measured as the proportion of immature oocytes that reach the blastocyst stage, rarely exceeds the 30–40% threshold [4], which means that the proportion of oocytes that fail to develop following in vitro maturation, fertilization, and culture is considerably large. Contrary to humans or mice, where eggs are mainly collected at the MII stage, in livestock species, the oocytes have to be matured in vitro due to the difficulty of obtaining a sufficient number of in vivo matured oocytes [5]. Additionally, given that the most frequent source of ovaries is slaughterhouse-derived animals, many important factors that influence oocyte quality, such as age of the donor, the stage of the estrous cycle, nutritional status, genetic potential, presence of a reproductive disorder, and others, are often unknown [6]. Therefore, it is almost impossible to avoid the retrieval of a heterogeneous population of oocytes that have a distinct ability to undergo maturation and support early embryonic development after fertilization, which is known as developmental competence or oocyte quality [7].

Considering that the intrinsic quality of the oocyte is one of the major factors affecting early embryonic development [8], and that embryo culture conditions have a crucial role in determining blastocyst quality [9], the precise selection of competent oocytes is vital for IVP technologies in livestock. Recently, the new arrival of bovine embryonic stem cells (ESCs) [10][11] emphasizes the already existing challenge in the selection of competent oocytes for the production of high-quality embryos through in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) or somatic cell nuclear transfer (SCNT), and derivation of pluripotent stem cell lines, with promising applications in research or industry, such as in vitro breeding programs [12]. Usually, for IVP and micromanipulation procedures (ICSI and SCNT), the choice of the oocytes lie in morphological features that are easily assessed with light microscopy [13]. The major difference and/or advantage of conventional IVF compared to micromanipulation procedures is that fertilization can occur during gamete co-incubation when the oocyte has reached or is close to nuclear and cytoplasmic maturity [14]. Conversely, during micromanipulation procedures, the operator must accurately assess the maturity of the oocyte and, therefore, its competence [15]. Because the criteria used for grading and selecting oocytes vary among researchers could be easily misinterpreted, and depend on the expert’s evaluation and experience, the identification of noninvasive cellular or molecular markers that predict oocyte competence is a major research goal [16][17]. Despite efforts for finding molecular factors associated with oocyte quality, it is still challenging to find a visual marker that accurately predicts embryonic competence.

2. Non-invasive Molecular Approaches

Many studies are being performed in mammals in order to find molecular markers predictive of oocyte quality. So far, most of the data show considerable variations, perhaps due to different experimental conditions and/or the criterion of quality/competence, resulting in varied scientific views.

2.1. Cell Death (Apoptosis) in Cumulus Cells

Because morphological evaluation prior to maturation does not allow to discriminate the atretic oocytes from healthier ones [18], one of the earlier noninvasive markers of oocyte competence was the level of apoptosis in CC, seen as DNA fragmentation, externalization of phosphatidylserine (EP), and/or the expression ratio of anti-apoptotic (Bcl-2) and pro-apoptotic (Bax) genes (BCL-2/BAX). Early studies found that the CC of bovine COCs undergoes progressive apoptosis during IVM [19], and this was negatively correlated with the oocyte developmental capacity [20]. However, results reported by Janowski et al. [21] supported the notion that follicular cells surrounding more competent oocytes have a higher degree of apoptosis. Later, Warzych et al. [22] showed that the level of apoptosis in CC was not associated with morphology or the oocyte meiotic stage, suggesting that the extent of apoptosis in CC is not a reliable quality marker for gamete competence. Similarly, the study of Anguita et al. [18] showed that embryonic developmental potential increased together with oocyte diameter, but this developmental competence was not associated with the incidence of apoptosis. Recently, another study indicated that the optimum control of meiosis, nuclear maturation, and developmental potential were not associated with DNA fragmentation in CC [23].

Similarly, in the human model, the majority of related studies have focused on granulosa cells (GC) isolated from FF during oocyte collection. Apoptosis, evaluated by EP, of GC was negatively associated with egg and embryo numbers in IVF/ICSI cycles, pregnancy rate, and live birth rate after IVF [24][25]. However, contrarily, it was also reported that the EP in GC is not related to follicular quality and oocyte competence during ICSI [26]. Thus, in the bovine and human models, it is still controversial whether apoptosis of GC and/or CC can impact the developmental potential of the associated oocyte.

2.2. Transcriptomic and Proteomic of Cumulus Cells

Many new genomic tools helped to deepen the understanding in the area of oocyte–cumulus communication, as well as molecular pathways required for the acquisition of competence in mammalian gametes and embryos. For instance, recent advances in RNA-Seq technology offer a global transcriptomic approach for identifying differentially expressed genes associated with competence and embryonic development.

Among the molecular approaches, the study of the transcriptomic profile of the surrounding cumulus is one of the most popular attempts at finding molecular markers associated with gamete competence in mammals. The “noninvasive” strategy is based on profiling the gene expression of a small biopsy before IVM, maintaining COC integrity, and following the embryonic development of the respective oocyte. This is also called “oocyte fate” [27]. Although several studies in cattle already found several genes in CCs from germinal vesicle (GV) [16][28][29][30][31][32][33][34][35][36][37] and MII oocytes [30][38] to be associated with oocyte competence, only a few reports matched the oocyte fate with the transcriptomic profile obtained from the CCs or granulosa cells. There is some consensus regarding pathways correlated positively with oocyte competence, including the cell cycle (CCND1, CCNB2, and CCNA2 genes) [29][31][39], cell growth and proliferation, (CD44, TGFB1, EGF, FGF11, PRL, and GH genes) [28][33][34][35][40], and steroidogenesis (HSD3B2 and CYP11A1 genes) [16][40]. On the contrary, genes related to cellular apoptosis would be associated with a low competence (ATRX, KRT8, ANGPT2, KCNJ8, and ANKRD1 genes) [27][33][38][41].

On the other hand, studies analyzing the proteomic profile of the cumulus–oocyte complex (COC) are scarce. Moreover, most of them have done invasive analysis in a pool of oocytes; thus, oocyte fate could not be followed. Nonetheless, the few studies described many proteins involved in cell signaling that may have a role in cumulus–oocyte communication and competence. Most of the proteins are involved in components of integrin, actin cytoskeleton, mitogen-activated protein kinases (MAPK) and phosphatidylinositol 3-kinase (PI3K) signaling pathways, extracellular matrix (ECM) receptor interactions, steroid biosynthesis, and glucose and carbohydrate metabolism, which may have implications in various reproductive processes such as oocyte development and maturation [42][43][44]. A recent study reported a highly sensitive approach to characterize the CC proteome from a single COC after in vivo or in vitro maturation [42]. This method shows the potential to directly connect the cumulus proteome to the developmental potential of the corresponding oocyte, as already performed at the gene expression level.

2.3. Follicular Fluid Analysis

It is well known that the composition of FF has an impact on the developmental capacity of the oocyte and, thus, the resulting embryo. Excellent articles reviewed the importance of FF on oocyte physiology and fertility [45][46][47]. This fluid contains proteins, cytokines, growth factors, steroids, metabolites, and other indeterminate factors [45]. Therefore, by studying its composition, it should be possible to predict oocyte competence and fertilization outcomes [48][49][50]. Metabolites in the FF, such as glucose and potassium, have already been positively associated with oocyte quality in cattle [51][52]. However, studies linking the FF features with the respective oocyte fate in bovines have not been performed yet. Reports in humans have positively associated the presence of anti-Müllerian hormone (AMH) in FF with the competence of the respective oocyte [53][54], although with some contradictory results [55][56]. Conversely, a recent study that used a large population of transferred embryos matching FF samples indicated that the AMH level in FF following withdrawal from the ovarian follicle is closely linked to the oocyte's competence, and it is a suitable predictor of a live birth after a single embryo transfer [57]. In the cow, it was already reported that AMH concentrations can be predictive of the number of ovulations and embryos produced in response to ovarian stimulation by FSH [58][59][60], making it a suitable molecule to be related to the oocyte competence.

In addition, other molecules in FF of cattle that show promising results are microRNAs (miRNAs). The bovine FF contains free miRNAs, as well as some associated with exosomes [61][62]. Recently, the study of Pasquariello et al. [63] showed, for the first time, the miRNA content of different populations of oocytes categorized according to their competence. Interestingly, they discovered that the most differentially expressed miRNAs (miR-24, miR-10a, and miR-320a) in FF found in highly competent follicles were part of the regulation of the neurotrophin signaling pathway, which supports follicle formation and development, as well as the TGF-βsignaling pathway that controls the production of ovarian peptide hormones. Therefore, linking FF molecules such as AMH or miRNAs with gamete competence is an encouraging strategy in the field of oocyte selection. However, we have to consider that it will be applicable only when the fast collection and analysis of FF from individual follicles become practicable.

3. Conclusions and Future Perspectives

The classification and selection of oocytes in livestock species for in vitro embryo production and for micromanipulation techniques, such as ICSI and SCNT, can be one of the most important steps to reach superior embryonic development and quality. Although more sophisticated methods (qRT-PCR, global transcriptomic, and proteomic analysis) have been studied since a few decades ago, the lack of a quick enough method producing reliable results hinders the implementation of these technologies. Moreover, molecular analysis requires high-tech equipment and technical staff that would be cost-ineffective in most research laboratories. Thus, although oocyte selection based on morphologic criteria appears to be insufficient to distinguish more competent gametes, in real practice, when 100–300 oocytes are waiting to be processed during micromanipulation experiments, it seems to be the only available strategy so far. Furthermore, studies that perform embryo transfers are also important to effectively evaluate developmental potential, as successful embryo implantation is highly dependent on the quality of the embryo and the intricate relationship it establishes with the uterine endometrium. Ultimately, with the advent of bovine embryonic stem cells, greater scrutiny of oocytes with high developmental potential is necessary, for the production of stable pluripotent stem cell lines to be used in basic science, forward and reverse genetics, epigenetics, gene imprinting, and the production of animal models with applications in animal production. Thus, in addition to improving the conditions to support in vitro maturation, the implementation of new tools for the assessment of gamete competence, together with studies decoding molecular cues in oocyte maturation, will improve our understanding of this complex process and will more precisely identify the synchrony between nuclear and cytoplasmic maturation in livestock species.

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