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Review Article

Cumulus-oocyte developmental competence: From morphological selection to molecular markers

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Abstract

The intrinsic quality of mammalian cumulus-oocyte complexes (COCs) is a determinant factor for pregnancy and fertility in general. The efficiency of assisted reproductive techniques required selection of good quality COCs. Despite the efforts that has been made during the last decades until now worldwide, there is no a reliable non-invasive method or even a reliable marker for oocyte selection. Generally, oocyte quality evaluated based on its morphological features such as thickness, compactness of the cumulus investment and the homogeneity of the ooplasm, which is relatively popular and convenient. However, results derived from this tool are often conflicting largely due to subjectivity and inaccuracy. Thus, the morphological evaluation alone is insufficient to distinguish competent oocytes that have the ability to bring about full-term pregnancy. Biochemical constituents of the follicular fluid represent sensors of the microenvironment condition surrounding the oocyte. Few efforts have given an attention for follicular fluid to be used as oocyte biomarker. Noteworthy, intensive application of assisted reproductive biotechnologies in human and domestic animal species require a good method for selecting good quality oocytes. Recently, global assessment strategies of omics approaches (transcriptomics, miRNAomics, proteomics, lipidomics and metabolomics) have been applied to profile the follicular fluid, oocytes, and granulosa or cumulus cells in several animal species in addition to human. Integration of more than one tool could be a window for finding reliable judging method. Although the great contribution of oocyte quality in controlling fertility the efforts done in finding reliable biological markers is still in the infancy stage. The current short review will shed highlight on attempts has been made in this field.

Oocyte developmental competence

The term "oocyte competence or quality" is the final measurement of its ability to achieve all cytoplasmic, nuclear and molecular events either in vivo or in vitro to bring a healthy offspring. Sirard, et al. [1] have defined the levels of competence as the ability of oocyte to resume meiosis, cleave following fertilization, develop and differentiate into blastocyst stage, induce pregnancy and finally bring healthy offspring.

Methods used for oocyte selection

There are many criteria (morphological, cellular, molecular) have been proposed to evaluate oocyte quality [2]. The main method of oocyte selection is done based on the morphological evaluation, which score COCs into four classes taken into consideration cytoplasm darkness, number of cumulus layers, extrusion of polar body and spindle formation [2,3]. However, this tool of oocyte selection is inconsistent and sometimes is

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controversial [2,3], but it a useful preselection tool that could be integrated into other methods. On the other hand, bovine follicle diameter [4] has been shown to be promising tool for oocyte quality screening. Moreover, evaluation of protein activity (glucose-6-phosphate dehydrogenase) was done using brilliant cresyl blue (BCB) staining, which was an effective tool to differentiate good and bad oocyte quality in different animal species. For example, this method was used to screening bovine [5,6], porcine [7], buffalo [8], equine [9], camel [10], goat [11], sheep [12] and mice COCs [13].

A positive relationship between the time of first cleavage post-insemination, and blastocyst rate was reported as effective criteria for bovine oocyte selection [14]. This idea was supported by the work done using time-lapse monitoring system that indicated that oocytes cleaving earliest after IVF being more likely to form blastocyst in good quality that successfully induced pregnancy than their late cleaving counterparts [15].

From molecular point of view, gene expression profiling of cumulus and the oocytes were considered as markers of the bovine oocyte quality [5,16-18]. Expression profile of key genes regulating expansion of cumulus cells (TNFAIP6) and maturation of oocyte (INHBA and FST) were over-expressed in bovine cumulus cells enclosed to COCs matured in vivo [19]. In human, expression of cumulus genes induced by the ovulatory LH peak namely amphiregulin (AREG), cyclooxygenase 2 (COX2 or PTGS2), and steroidogenic acute regulatory protein (STAR) were among molecular markers of COCs nuclear maturation [20,21]. Interestingly, a cumulus expansion regulating gene known as pentraxin 3 (PTX3) was described to be candidate for selecting human oocytes with high ability for pregnancy success [22]. Interestingly, Gasca, et al. [23] have identified regulatory genes (BARD1, RBL2, RBBP7, BUB3 and BUB1B) involved in human COCs maturation.

Distinct sets of candidate genes have identified in bovine oocytes selected according to follicular wave (growth vs. dominance phase) and Brilliant Cresyl Blue (BCB) staining of the first follicular wave [5,24]. Genes regulating protein biosynthesis (RPL24, RPS14, RPS15 and EEF1A1) and mitochondrial activity (ATP5A1) were upregulated in developmentally competent oocyte [5,24]. A cell division cycle 5-like protein (CDC5L) was described to be essential molecular gene for maturation and subsequent embryonic divisions in porcine oocyte selected with BCB test [25]. While, a candidate gene encodes for protein that functions, as zinc transporter (SLC39A8) is upregulated in cumulus cells of bovine [26] and mice oocytes [27]. Recently, STAT3 was identified as a candidate gene of oocyte developmental potential in a study done in our lab [28].

Concluding remarks

Poor oocyte quality reduced fertility rate in vivo and efficiency of in vitro reproductive techniques. Therefore, integration of different methods of COCs selection could be an effective way to increase developmental capacity of oocytes. Meta-analysis of previously discovered molecular markers in the cumulus-oocyte complexes will improve our understanding on the networks of signals that regulate developmental potential and could lead to development of a novel tool for oocyte selection.

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