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Gene expression of granulosa and cumulus cells: The prospect in predicting the quality and developmental competence of oocytes *in vitro* maturation

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Abstract: *In vitro* maturation (IVM), a promising assisted reproductive technology (ART), has been evolving in clinical trials and applications. There is a huge potential demand for IVM in clinical practice because it reduces the stimulation of gonadotropins to patients and provides evidence for the safety of neonatal birth. Unfortunately, the maturation rate of oocytes *in vitro* is not as high as it is *in vivo* due to a different microenvironment. Moreover, there are still controversies in predicting the developmental capability of oocytes in IVM. The granulosa cells (GCs) and cumulus cells (CCs), closely surrounding the oocytes, play a critical role in oocytes development, while some studies have shown that they can reflect the quality of oocytes. Many studies have been conducted in terms of oocyte quality in transcriptional level in GCs and CCs of mice, *Xenopus africanus*, and *Homo sapiens*, which provides important enlightenment for the successful clinical application of IVM. However, no comprehensive reviews about how gene expression profiles affect oocytes quality have been reported. This review aimed to elucidate the gene expression profiles of GCs and CCs that have effects on the quality and developmental competence of oocytes maturation *in vitro*. And we also put forward a possible idea for ART in the future, integrating all gene expression profiles of GCs and CCs and predicting the quality of the oocytes.

Introduction

The developmental competence of oocytes refers to the ability of the oocyte to mature and then successfully fertilize, cleave, and enter the blastocyst stage to produce high-quality embryos. This sequence of events is continuous and precisely controlled *in vitro*, and the success of one does not guarantee the success of the next, making it difficult to cultivate *in vitro*. Experiments on cows have shown that 60% of oocytes *in vitro* reach the blastocyst stage, while less than 40% *in vitro* maturation (IVM) of oocytes reach the blastocyst stage (Marei *et al.*, 2014). The success rate of IVM for human oocyte is lower. Oocyte IVM refers to the whole process in which immature oocytes (germinal vesicle, GV stage) recover from small-sized follicles, mature, fertilize, and develop into embryo under the laboratory-culture conditions. The clinical definition of IVM of oocyte has been proposed in recent years, that is, oocyte is extracted from small or medium-sized follicles for culture before the average diameter of the largest ovarian follicle reaches 13 mm (Dahan *et al.*, 2016). IVM of the human oocytes has had profound clinical implications since the first live birth after the IVM procedure was reported in 1991 (Cha *et al.*, 1991). However, the success rate of IVM of human oocytes is not as high as it is in animals. Additionally, selecting embryos with high transplantation potential is the crux of the IVM. Traditional selection methods are based on morphological assessment, which includes growth rate, developmental diameter, early cleavage, and degree of division (Ebner *et al.*, 2003). Obviously, these assessments are invasive and imprecise. In recent years, quantitative methods such as time-lapse imaging of embryonic cell division dynamics and genetic screening of blastocysts have been developed. However, further studies are needed to evaluate the predictive value of other markers for human oocyte quality. Since a crucial role of granulosa cells (GCs) and cumulus cells (CCs) have on the development of

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oocytes *in vitro*, many researchers concentrate on these clusters of cells and apply them to IVM. Furthermore, there is a growing awareness that the gene expression profile of GCs and CCs are extremely critical in predicting the quality of oocytes *in vitro* maturation (Tabibnejad *et al*., 2019).

Oocytes arrested at metaphase-I stage are surrounded by GCs during follicular development and formation. The CCs involved in oocyte proliferation and development originate from GCs, which differentiate into mural granulosa cells (MGCs) and CCs during the development of antral follicles. One of the major functions of CCs is transmitting nutrients and metabolites to the oocytes to maintain the various stages of oocyte growth and development (Lonergan and Fair, 2016). Gene expression analysis of GCs and CCs as predictors of oocyte quality and developmental potential has received more and more attention in recent years. Brown *et al*. (2017) proposed that the matured CCs *in vitro* exhibited differential gene expression patterns compared with *in vitro* derived cumulus-oocyte complexes (COCs). This might be the primary reason for partial function defects of CCs in IVM, resulting in reduced oocyte quality. Previous articles explored the oocyte capacity by investigating the gene expression of CCs. This paper advanced a possible idea for assisted reproductive technology, updating all gene expression profiles of GCs and CCs that may be used to better predict oocyte quality. Combining one or more of these factors into a usable culture medium may increase the success rate of human clinical IVM therapy. Immediately afterward, IVM therapy was combined with standard IVF to promote embryo maturation and increase the live birth rate. Here, we attempted to expound the gene expression profiles of GCs and CCs at IVM system from a new perspective, to explore the most favorable genes for oocyte maturation, which could provide new ideas for solving clinical difficulties.

Cellular growth and proliferation

Just before ovulation, human oocytes will grow to approximately 100 μm in diameter (Mehlmann, 2005). The first thing that happens when a woman enters puberty is a surge in luteinizing hormone (LH), which affects oocyte meiosis and cytoplasmic maturation, leading to ovulation (Pan and Li, 2019). In the process of growth and proliferation, oocytes acquire meiotic ability (nuclear maturation) first and then developmental ability (cytoplasmic maturation), both of which depend on the surrounding CCs (Tanghe *et al*., 2002). Initially, the transcripts of gremlin1 (GREM1), hyaluronic acid synthase 2 (HAS2), and cyclooxygenase 2 (COX2/PTGS2) in CCs were confirmed to be related to the growth and development of oocyte (Dunning *et al*., 2015). HAS2 is responsible for the formation of extracellular matrix (ECM) during ovulation. Meanwhile, HAS2 is specifically expressed by CCs under the joint action of growth differentiation factor-9 (GDF-9), and oocytes secreted follicle-stimulating hormone (FSH) (Dragovic *et al*., 2005), suggesting that its gene expression is associated with oocytes quality. Subsequently, the expression of various target genes in human CCs was studied (Feuerstein *et al*., 2007), such as Steroidogenic Acute Regulatory protein (STAR), COX2 or PTGS2, Amphiregulin (AREG), Stearoyl-Coenzyme A Desaturase 1 and 5 (SCD1 and SCD5). It has been observed that the nuclear maturation of oocytes accompanies the active gene expressions mentioned above. Then, it was reported that Tumor Necrosis Factor α-induced protein 6 (TNFAIP6), Pentraxin-3 (PTX3), and several EGF-like growth factors (epiregulin, amphiregulin, and betacellulin) were inhibited *iv vitro*, which did not occur in mature oocytes *iv vivo* (Ouandaogo *et al*., 2012). This might explain the low IVM rate of oocytes. More and more evidence showed that AREG likely played an important role in oocyte growth (Brown *et al*., 2017). AREG protein was revealed to be more abundant than other EGF-like factors in mature human follicular fluid (Peluffo *et al*., 2012; Zamah *et al*., 2010). Maternal Antigen That Embryos Require (MATER) in human CCs also has been reported that can affect follicular and oocyte growth (Sena *et al*., 2009). The expression of Versican in human CCs has been detected to be related to successful ART outcomes (Ekart *et al*., 2013; Gebhardt *et al*., 2011; Hammond *et al*., 2015; Wathlet *et al*., 2011). The ability of Versican to activate the EGF receptor (EGFR) in CCs and to stimulate COCs maturation was also found recently (Dunning *et al*., 2007; Dunning *et al*., 2015). All of these indicated that the Versican gene in the GCs has a role in promoting oocyte growth, proliferation, and maturation.

In the process of follicular development and formation, oocytes are initially surrounded by GCs, subsequently some of which form CCs. GCs discarded at *iv vitro* fertilization (IVF) provide a good tool for studying follicle microenvironment. Changes in gene expression patterns of GCs can reflect the stress response of cells to the follicle microenvironment at a specific moment and further trace the relevant information of oocyte development. Some studies indicated that granulosa derived factors may activate COCs maturation and promote the growth and proliferation of oocytes under the induction of CCs (Huang *et al*., 2015; Shimada *et al*., 2006), so their low expression in IVM may be another key factor leading to poor quality results. Neuregulin 1 (NRG1) in GCs has been shown to inhibit the growth and proliferation of oocytes, indicating that it can be acted as an important granulosa derived factor (Kawashima *et al*., 2014). Since NRG1 is not a product of the cumulus gene, no NRG1 was found in the differential expression gene of IVM COCs, but the deficiency of NRG1 was caused by the lack of GCs, which may be the reason for the abnormal proliferation of IVM oocytes (Kawashima *et al*., 2014). In recent years, it has been found that the activation of EGFR in CCs contributes to the stimulation of phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB, AKT) signaling pathway in oocytes. This pathway governs oocyte growth, survival, and proliferation by maintaining genomic integrity (Chen *et al*., 2013; Franciosi *et al*., 2016; Maidarti *et al*., 2020). The maturation of the oocyte is finally triggered by the maturation promoting factor (MPF) (Gerhart *et al*., 1984), whose activity is regulated by mitogen-activated protein kinase (MAPK).

Cell cycle

One indispensable step that occurs before ovulation is the restoration of meiosis I (MI), the completion of the cell cycle. We attempt to illuminate the effect of differential gene

expression in CCs on it. Meiosis begins between 11 and 12 weeks of gestation in the ovary of a human embryo (Gondos *et al.*, 1986). There are approximately 2 million primary oocytes in the two ovaries of newborn babies, all of which enter the MI but without developmental abilities at this stage. Under the influence of pituitary gonadotropin, FSH and LH, these primary oocytes further develop and ovulate during sexual maturation. In most cases, oocytes maturation takes about one-month, during which CCs gene expression remains active (Hunt and Hassold, 2008; Tatone *et al.*, 2008). Metaphase of meiosis II (MII) recovers after oocytes are fertilized by sperm. However, meiosis is spontaneously resumed when oocytes are removed from the follicular environment (Pincus and Enzmann, 1935). Therefore, the cell cycle of oocytes in IVM is totally different from that *in vivo*. Another study confirmed that cyclic adenosine monophosphate (cAMP) generated by CCs might be a pivotal factor controlling this process, and negatively regulates the germinal vesicles breakdown (GVBD) by activating cAMP-dependent protein kinase (PKA) (Eppig and Downs, 1984). Low cAMP concentration during IVM improves oocyte quality and subsequent embryonic development (Shu *et al.*, 2008).

It has been revealed that CCs of IVM are higher mitotic than CCs *in vivo*, whose specific gene expression had different effects on the oocytes cycle (Ouandaogo *et al.*, 2011). With the development and application of biotechnology, microarray and real-time PCR have been widely used in the field of gene research (van Montfoort *et al.*, 2008). It was found that the expression of some genes can negatively regulate the maturation of oocytes, including cyclin D2 (CCND2), tripartite motif-containing 28 (TRIM28), 7 dehyro-cholesterol reductase (DHCR7), catenin, cadherin associated protein, delta 1 (CTNND1). To further determine which genes are necessary for maintaining the normal cell cycle of the oocyte in CCs, Hamel *et al.* (2008) reported a set of oocyte markers. Finally, cell division cycle 42 (CDC42) was identified (Hamel *et al.*, 2008). Activation of CDC42 results in the polarity establishment and meiotic division of oocytes (Zhang *et al.*, 2017). Subsequently, a lot of genes are detected with an up-regulation in IVM oocyte by microarray technique, which includes cyclinV2 (CCNV2), cyclinB1 (CCNB1), cyclinE2 (CCNE2), and other cyclin and cyclin-dependent kinase (CDK) genes (Ouandaogo *et al.*, 2012). Specifically, PKA is reduced right after the cAMP decrease in oocytes *in vitro*, resulting in the dephosphorylation of CDC2. CDK1 and CCNB are also activated subsequently, and then MI is completed.

In addition, some important genes were found to be involved in the cell cycle of human oocytes and CCs, including breast cancer 1 & 2 (BRCA1 & 2), breast cancer1-associated RING domain1 (BARD1), retinoblastoma-like 2 (RBL2), retinoblastoma binding protein 7 (RBBP7), budding uninhibited by benzimidazoles 3 (BUB3) and spindle checkpoint protein (BUB1B), mitotic arrest deficient protein2 (MAD2) (Gasca *et al.*, 2007).

Extracellular matrix

With a surge in LH, ovulation is not the only event. The ECM, which is activated in COCs, also known as cumulus expansion (or mucification), relies on a cascade of specific signals within the cell to induce expression of related genes (Russell and Salustri, 2006). Successful expression of ECM has a positive effect on oocytes maturation rate, especially in IVM. Proper composition and assembly of the ECM are also crucial for the developmental competence of oocytes. Its active components come from a variety of sources, such as direct synthesis by CCs under the control of endocrine and oocyte-derived factors, or entry into follicles through plasma (Chang *et al.*, 2002; Eppig, 1982; Eppig, 1991; Vanderhyden *et al.*, 2003). The ECM mainly consists of hyaluronic acid (HA), PTX3, TNFAIP6, and the heavy chains (HCs) of serum-derived inter-α-inhibitor proteins. The expansion of the cumulus is accomplished by the synthesis of HA and the assembly of actin microfilaments to induce the comprehensive rearrangement of the cytoskeleton so that tightly packed CCs are transformed into a greater mass of mucous cells (Kidder and Vanderhyden, 2010). Ovulation is the extrusion of one or two of the most optimal oocytes from the follicular fluid when cumulus expansion and ECM formation are of the essence in this condition. This expanded process would be completed by two methods, such as oocyte secretion of paracrine factor and gonadotropin or EGF-like peptide stimulation (Fig. 1).

As an oocyte secretion factor, GDF-9 is extremely significant in the formation of ECM (Elvin *et al.*, 1999a; Sutton *et al.*, 2003). This secretory factor works associated

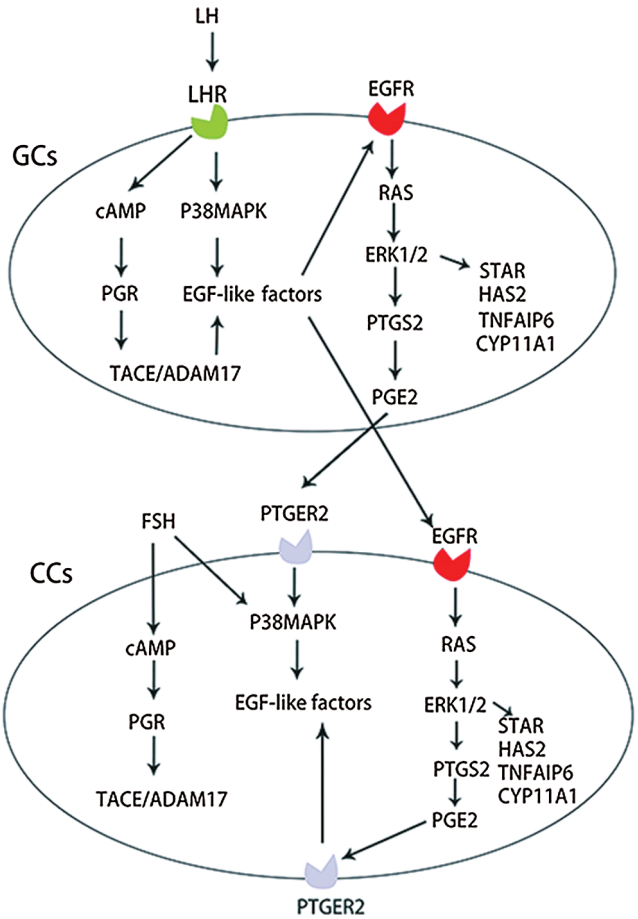

FIGURE 1. Granulosa cells and cumulus cells promote the formation of the extracellular matrix through an endocrine pathway.

with its receptor Bone Morphogenetic Protein Receptor Type 2 (BMPR2), which is highly expressed in CCs (Assou *et al.*, 2006). It induces a cascade of reactions involving downstream genes (Sanfins *et al.*, 2018). This process initiates the secretion of ECM substances, such as HA, TNFAIP6, and PTX3 (Hussein *et al.*, 2006). Therefore, we concluded that the upregulation of the GDF9 receptor in CCs is related to quality, especially during *in vitro* maturation. In addition, the role of granulosa-derived Versican has been revealed in the cumulus expansion (Dunning *et al.*, 2015). A surge of LH induced a rapid response of Versican in GCs, which was transmitted to CCs. At the same time, EGF-like factors were found to promote oocyte growth and maturation by inducing the expression of COX-2. The most critical role of EGF-like factors is to promote the cumulus expansion. Reported EGF-like factors include EREG, AREG, BTC (Liu *et al.*, 2010; Park *et al.*, 2004), HAS2, and TNFAIP6 (Fülöp *et al.*, 2003; Park *et al.*, 2004). These factors work via up-regulation of prostaglandin E2 (PGE2) receptor in the CCs, this process is essential for ECM formation and oocytes maturation (Ben-Ami *et al.*, 2006; Liu *et al.*, 2010). Moreover, these factors also play a direct role in cumulus expansion through PGE2 (Niringiyumukiza *et al.*, 2018). EGF-L factors and CCs respond to LH-surge and gonadotropin /FSH signals, respectively, resulting in increased oocyte developmental competence (Diaz *et al.*, 2006; Dragovic *et al.*, 2005; Dragovic *et al.*, 2007). Although the mechanisms of LH and FSH remain unknown, both tyrosine kinases or cAMP-dependent tyrosine kinases activated MAPK and extracellular regulated protein kinases (ERK) in CCs have been reported (Su *et al.*, 2002). EGF, FSH, or cAMP-induced cumulus amplification and ECM gene expression were restrained by Erks inhibitors (Ochsner *et al.*, 2003; Su *et al.*, 2002). Cumulus expansion and oocytes maturation could be inhibited by loss of function of conditional erk1/2. ECM formation is consequently inhibited, further supporting the physiological relevance of these factors. Progesterone induced TNFα-converting enzyme/A disintegrin and metalloproteinase domain 17 (TACE/ADAM17) can produce EGF domain in CCs, thus enhancing the functional changes of the CCs (Yamashita *et al.*, 2010; Yamashita *et al.*, 2014). In addition, a key enzyme in the process of ECM formation is PTX3 produced by human GCs, and PTX3 is required for the production of oocytes with high development potential and quality (Huang *et al.*, 2013). Research indicated that TGF-β1 regulates the expression of PTX3. What is noteworthy is that some changes in ECM components did not adversely affect oocyte growth, maturation, or ovulation (Ploutarchou *et al.*, 2015).

Metabolism

The development and maturation of oocyte are dependent on ATP which comes from highly active energy metabolism. It is the main energy procedure that oocytes produce ATP by the mitochondria oxidative phosphorylation with the glucose and/or its intermediate product, acetylformic acid, as substrate. In addition, fatty acids and amino acids, steroids, hemoglobin, glutathione peroxidase are also metabolic substrates in the oocyte (Thompson *et al.*, 2007). Besides providing energy indirectly, those metabolites and intermediates also play roles in signal transduction, osmoregulation, and so on, guaranteeing the maturation of the oocyte nucleus and cytoplasm. Oocytes are precisely controlled by CCs and present different metabolic requirements (Assou *et al.*, 2010). The metabolites of CCs are essential stimuli for bi-directional communication among the oocytes and cumulus vestment (Albertini *et al.*, 2001; Eppig, 1991; Matzuk *et al.*, 2002). CCs are taken more and more consideration by researchers in providing nutrients and substrates for oocytes maturation over the past two decades (Dumesic *et al.*, 2015). Studying the metabolism of oocyte and CCs is helpful to improve the oocyte quality and IVM efficiency (Eppig, 2005; Preis *et al.*, 2005; Su *et al.*, 2009; Sutton-McDowall *et al.*, 2004). Oocyte quality is also affected by phosphoglycerate kinase1 (PGK1), which encodes a transferase that plays an important role in the glycolytic pathway. Glycolysis is critical to the maturation and ability of oocytes, but in the final stage of follicular development, oocytes do not oxidize glucose during glycolysis and are highly dependent on the glycolysis products provided by GCs for energy (Gu *et al.*, 2015). Therefore, upregulating the expression of PGK1 in GCs during IVM condition can improve glycogenesis and affect the maturation and oocyte ability.

More glycolytic enzymes are active in CCs than oocytes, while the deficiency of glycolysis in the IVM system led to the lack of oocyte development ability, suggesting that the glycolytic level of CCs was associated with the quality of oocytes (Brown *et al.*, 2017). Glycolysis has been reported to involve the expression of glucose transporter 1 (SLC2A1), D—lactate dehydrogenase (LDHD), Enolase 2 (ENO2), hexokinase (HK2) (Kind *et al.*, 2013), and PGK1 (Hamel *et al.*, 2010). Glucose– and glutamine–dependent HA matrix is largely inhibited by down-regulating glutamine-fructose-6-phosphate transaminase (GFTP1) and HAS2 in IVM CCs (Caixeta *et al.*, 2013). Since FSH is a potent stimulator of glucose metabolism and nuclear maturation of CCs within COCs, so it is routinely added to the IVM system (Downs *et al.*, 1996; Sutton-McDowall *et al.*, 2004). Another important glycogen metabolism pathway is gluconeogenesis, in which the phosphoenolpyruvate carboxykinase 1 (PCK1) expressed in CCs participates. The cytoplasmic enzyme encoded by this gene, together with GTP, catalyzes oxaloacetic acid to form phosphoenolpyruvate to produce high-quality oocytes (Assou *et al.*, 2008). An emerging interest is that the reduction of carbonyl reductase 3 (CBR3) in CCs negatively regulate oocytes maturation (Tatone *et al.*, 2010; Tatone *et al.*, 2011).

β-oxidation is another crucial energy source for oocytes maturation. A high-quality oocyte is involved in the resumption of MI and the completion of MII, which include the proliferation of GCs, the formation of ECM, and the rearrangement of chromatin, with a large amount of ATP to consume (Dunning *et al.*, 2014). 106 ATPs are produced from the oxidation of a fatty acid compared with about 30 ATPs from glucose. Therefore, the significance of β-oxidation in oocyte maturation is becoming increasingly recognized (Brown *et al.*, 2017; Zarezadeh *et al.*, 2019).

β-oxidation mainly occurs in CCs (Dunning *et al.*, 2014), which inspired us to explore the differential expression of genes involved in CC fatty acid metabolism *in vitro* and *in vivo* maturation. There were microarray evidences that the expression of Long-chain acyl-CoA synthetase1 (ACSL1), Long-chain acyl-CoA synthetase4 (ACSL4), arachidonate 5-lipoxygenase activating protein (ALOX5AP), and lysophosphatidylglycerol acyltransferase 1 (LPGAT1) in human CCs are reduced at IVM system (Kind *et al.*, 2013; Ouandaogo *et al.*, 2012), leading the poor oocyte quality. ACSL is a family of lipid metabolism-related enzymes. In *Xenopus*, suppression of ACSL1 by knocking out its transcripts leads to abnormal acceleration of oocyte maturation. Interestingly, ACSL1 activates the G protein-coupled receptor3 (GPR3)-G-protein alpha S subunit (Gαs)-adenylyl cyclase (AC) signaling pathway, which maintains a high level of cAMP that is essential for arresting oocytes (Wang *et al.*, 2012). This finding is supported by the fact that a surge in LH *in vivo* causes a significant increase in the expression of the beta oxidation-related genes in COCs (Dunning *et al.*, 2010). Another research demonstrated that SCD1 and SCD5 also play a pivotal role in the lipid metabolism of oocytes (Feuerstein *et al.*, 2007).

Amino acids also play an important role in oocytes through a succession of specific transport systems. However, genes involved in the regulation of amino acid metabolism in CCs remain largely unknown. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) also play different roles in oocytes and CCs during IVM (Cetica *et al.*, 2003).

Steroid hormones regulate oocytes in a variety of ways. In follicular fluid, for example, these hormones work directly on oocyte through blood circulation, or work by affecting CCs and cytokines. Steroid-related genes are highly expressed in CCs *in vivo*, whereas IVM is the opposite (Ouandaogo *et al.*, 2012). This inspired us to attempt to illustrate the differential expression of steroid-related genes of CCs *in vivo* and *in vitro* maturation of oocytes. Estrogen is one of the most important steroids, whose synthesis is a clear sign of healthy communication between oocytes and CCs (Kidder and Vanderhyden, 2010). Therefore, it is necessary to further clarify the regulation mechanism of estrogen acting on oocyte matured *in vitro* to establish an excellent oocyte IVM system. Cholesterol side-chain cleavage-enzyme (CYP19A1) metabolizes androgens into estradiol-17b (Hamel *et al.*, 2008), and high levels of estradiol promote the synthesis of c-type natriuretic peptide (NPPC) and natriuretic peptide receptor 2 (NPR2), which is an important factor controlling the arrest and recovery of meiosis of oocytes (Lee *et al.*, 2013). It has been confirmed that the low expression of CYP19A1 during IVM condition will result in the reduction of progesterone and estradiol-17b levels in GCs conditioned medium, as well as low-quality oocytes (Nandi *et al.*, 2018). Microarray analysis confirmed that DHCR7 is involved in the synthesis of estrogen, and heat shock protein beta-1 (HSPB1) acts as a corepressor for estrogen signaling (van Montfoort *et al.*, 2008). In addition, estrogen receptor also plays an important role in mediating the genomic and non-genomic effects of estrogen. There were two types of estrogen nuclear receptors, estrogen receptor-α (ERα) and estrogen receptor-β (ERβ), both of which bound to estrogen and acted as its transcription factor (Hewitt *et al.*, 2016). G protein-coupled receptor 30 (GPR30, has been named G-protein coupled estrogen receptor, GPER) locates on the oocyte membrane and expresses during oocyte maturation, suggesting that GPR30 may play an important role in regulating oocyte maturation (Li *et al.*, 2013).

Cholesterol, a precursor of steroid hormone synthesis, can also regulate the content and biological activity of steroid hormones *in vivo*. The transport of cholesterol was mainly mediated by protein in the process of follicular steroid synthesis. Previous studies have reported that intracytoplasmic cholesterol can be transported by Sterol regulatory element-binding protein-2 (SREBP-2) and cholesterol-specific START domain containing 4 (STARD4) to the outer membrane of mitochondria, and then transported by STAR to the inner membrane of mitochondria, further converted into progesterone (Feuerstein *et al.*, 2007; Rimon *et al.*, 2004). Thereby increasing the progesterone content in the follicular fluid can regulate oocyte maturation through affecting mitochondria development. Interestingly, the expression of some genes remains unaffected by IVM during the conversion of cholesterol to progesterone (Coticchio *et al.*, 2017). Moreover, ferredoxin 1 (FDX1) and hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1 (3βHSD) have been found to be responsible for progesterone synthesis (Hamel *et al.*, 2008).

We still have little information about the function of hemoglobin in the COCs (Thompson *et al.*, 2015). It mainly plays a role during ovulation, involved in oxygen binding and dissociation (Brown *et al.*, 2017). It is also thought to act as an antioxidant (Thompson *et al.*, 2015). Microarray analysis showed that hemoglobin A1 (HBA-c1) is significantly differentially expressed between *in vivo* and IVM (Brown *et al.*, 2015; Kind *et al.*, 2013; Brown *et al.*, 2017). In addition, genes involved in oxygen transport in CCs include endothelin 2 (EDN2), Bnip3 (NIP3), B-cell lymphoma-2 (BCL2), LDHD, N-myc downstream-regulated gene 1 (NDRG1), vascular endothelial growth factor A (VEGFA), and HK2 are down-regulated during IVM (Kind *et al.*, 2013).

The expression of glutathione peroxidase-1 (GPX1) in human oocytes has been reported to be related to the gamete quality (Ceko *et al.*, 2015). Therefore, amino acids, especially cysteine, should be added into IVM medium, in clinical application, to increase the level of glutathione in oocytes.

Cell-to-cell signaling and interaction

The critical of immature oocyte IVM is to simulate the microendocrine environment of follicular development in the human body, which consists of follicular fluid, CCs, GCs, and theca cells. And in this microenvironment, cell-to-cell signaling, and interaction is indispensable (Anderson *et al.*, 2018; Cui *et al.*, 2018; Buratini and Comizzoli, 2019; Dumesic *et al.*, 2015; Russell *et al.*, 2016). Oocyte development is a highly coordinated and interdependent event. Hence, investigating differential gene expression during CCs development and intercellular various modes of action is vital for inspecting oocytes developmental potential

(Barrett and Albertini, 2010; Coticchio *et al.*, 2015; Su *et al.*, 2008; Sugiura *et al.*, 2007; Wigglesworth *et al.*, 2013). To date, intercellular communication is mainly conducted by oocyte secretion factors (OSF) and gap junctions. The interactions between oocytes and GCs/CCs, including material and small molecule signals shuttling between them, are mediated through gap junctions and paracrine pathways. CCs proliferation is promoted by OSF through direct interactions, and cumulus expansion is also promoted by the synthesis of PTGS2 and HAS2. CCs also provide small molecules such as pyruvate, cholesterol, and alanine to promote the development of oocytes and synthesize EGF-like peptide to reduce connexins 43(Cx43), also referred to as Gap Junction alpha1 (GJA1), thereby reducing intracellular cAMP and promoting oocyte maturation (Fig. 2).

One example of the bidirectional communication methods is that GCs and CCs promote the secretion of bioactive molecules of oocytes by transmitting signals. These factors in turn act on GCs and CCs to play a regulatory role, thus completing the signal circuit (Cakmak *et al.*, 2016). Two essential OSFs, GDF9 and bone morphogenetic protein 15 (BMP15) can regulate the signaling pathway by impacting the pivotal genes of CCs (Gilchrist *et al.*, 2008). Additionally, they also boost the proliferation and expansion of CCs, regulate CCs metabolism, prevent CCs apoptosis, and regulate the function of GCs (Gilchrist *et al.*, 2008; Vanderhyden *et al.*, 2003). GDF9 induces expression of multiple genes that are required for mouse cumulus expansion, including Has2, Ptegr2, smad2/3, Cyp19a1, Prdx2, Tnfaip6, Ptx3, and Ptgs2 (Elvin *et al.*, 1999b; Varani *et al.*, 2002). Moreover, this factor appeared to be localized only to oocytes (Aaltonen *et al.*, 1999). Detection of the expression of GDF9 downstream target genes in CCs was in favor of predicting the development quality of oocytes (McKenzie *et al.*, 2004). A second oocyte-specific factor, BMP15 (also known as GDF9b), has also been reported (Dube *et al.*, 1998; Laitinen *et al.*, 1998). Expectedly, it has been testified that BMP15 and GDF9 are closely interrelated (Persani *et al.*, 2014). Recently, GDF9 and BMP15 were found through the PI3K/AKT and Smad2/3 pathways synergistically recruit the coactivator p300 on the Anti–Müllerian hormone (AMH) promoter region that facilitates acetylation of histone 3 lysine 27 (H3K27ac), promoting the secretion of AMH from GCs (Roy *et al.*, 2018). This process can promote the communication between oocytes, CCs, and GCs *in vitro*, improving the developmental competence of oocytes under IVM conditions. BMP15 not only promotes the secretion of estrogen and FSH (Stephens and Johnson, 2016; Sutton-McDowall *et al.*, 2015) but also plays an important role in regulating the signaling of GCs (Persani *et al.*, 2014). Furthermore, BMP15 can prevent GCs apoptosis and facilitate the maturation of oocytes (Belli and Shimasaki, 2018; Persani *et al.*, 2014). And the functions of BMP15 in humans have been well-reviewed (Elisa *et al.*, 2004).

Another way of signaling and interaction between cells is gap junctions. It has been reported that gap junctions existed in CCs-oocytes (Amsterdam *et al.*, 1976; Anderson and Albertini, 1976; Hyttel *et al.*, 1989) and GCs-oocytes (Edry *et al.*, 2006). They are specialized structures that occur at spots of extra tight intercellular connection, and they are composed of cell-cell channels that permit the direct transmitting of small molecules between cells (Kidder and Vanderhyden, 2010). Small molecules transferred from CCs or GCs to oocytes included Na+, Cl–, cAMP, cGMP, various ribonucleosides, etc. (Arellano *et al.*, 2002; Bornslaeger and Schultz, 1985; Brower and Schultz, 1982; Colonna and Mangia, 1983; Heller and Schultz, 1980; Moor *et al.*, 1980; Norris *et al.*, 2009). Fully developed GCs use gap junctions to adjust the pH of oocytes via ion transporters (Fitzharris and Baltz, 2006). CX43, a major component of human gap junctions, affects the development ability of human oocytes (Hasegawa *et al.*, 2007). Assou *et al.* (2010) identified Cx37 (GJA4) and Cx40 (GJA5) participated in gap junction using microarrays.

Apoptosis

Oocyte will undergo apoptosis programmed cell death (PCD), if it does not fertilize in time in the IVM system (Haouzi *et al.*, 2008; Miao *et al.*, 2005). Early apoptotic signals are vital for predicting the quality of oocyte development (Wu *et al.*, 2017). The control of oocyte apoptosis *in vitro* is important for ART. Previous studies have shown that CCs accelerated

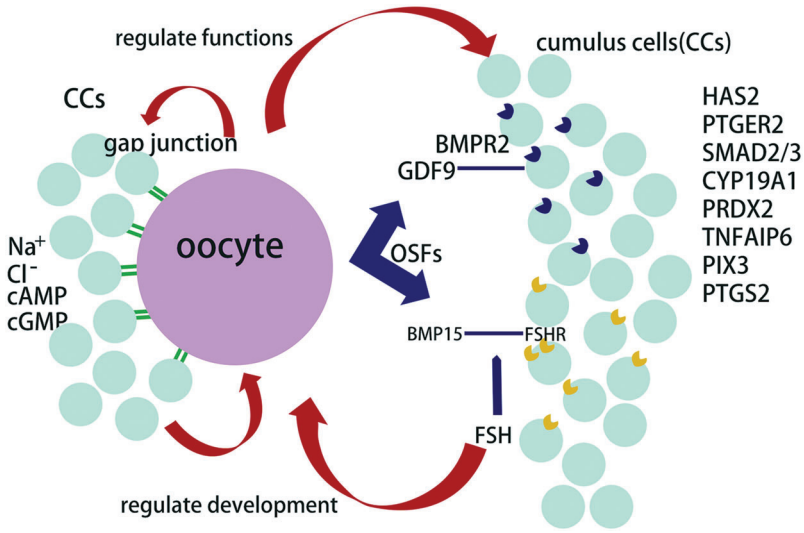

FIGURE 2. Oocytes and cumulus cells regulate each other's development and function by bidirectional communication.

TABLE 1

Key genes that usually used to predict the quality of IVM oocytes

GCs/CCs Genes	Effects on oocytes	References
GREM1	Cellular growth and proliferation	(Dunning *et al.*, 2015)
HAS2	Cellular growth and proliferation	(Dunning *et al.*, 2015)
COX2/PTGS2	Extracellular matrix	(Fülöp *et al.*, 2003; Park *et al.*, 2004)
EGFR	Metabolism	(Caixeta *et al.*, 2013)
cAMP	Cellular growth and proliferation	(Dunning *et al.*, 2015)
CDC42	Extracellular matrix	(Fülöp *et al.*, 2003; Park *et al.*, 2004)
GDF-9	Cellular growth and proliferation	(Chen *et al.*, 2013; Franciosi *et al.*, 2016; Maidarti *et al.*, 2020)
PTX3	Cell cycle	(Shu *et al.*, 2008)
ACSL	Cell cycle	(Zhang *et al.*, 2017)
CYP19A1	Extracellular matrix	(Elvin *et al.*, 1999a; Sutton *et al.*, 2003)
BMP15	Cell-to-cell signaling and interaction	(Gilchrist *et al.*, 2008; Roy *et al.*, 2018)
Caspase 9	Extracellular matrix	(Huang *et al.*, 2013)
FAS	Metabolism	(Kind *et al.*, 2013; Ouandaogo *et al.*, 2012; Wang *et al.*, 2012)
	Metabolism	(Hamel *et al.*, 2008)
	Cell-to-cell signaling and interaction	(Nandi *et al.*, 2018)
	Apoptosis	(Gilchrist *et al.*, 2008; Roy *et al.*, 2018)
	Apoptosis	(Zhao *et al.*, 2019)
		(Zhao *et al.*, 2019)

the process of oocytes apoptosis (Miao *et al.*, 2005; Qiao *et al.*, 2008). Strong evidence has supported them via the expression of soluble TNFα (sTNFα), soluble Fas ligand (sFASL), BCL2L11, and BCL10 in CCs increased, thus induced the apoptosis of oocytes (Assou *et al.*, 2008; Haouzi *et al.*, 2008; Kong *et al.*, 2018). In addition, TNFSF13 encodes a protein in the tumor necrosis factor (TNF) ligand family and up-regulates the BCL2L11 (Assou *et al.*, 2006). In recent years, more and more researches have been done on neurotropins (NTs) in the field of female reproduction. Among them, brain-derived neurotrophic factor (BDNF) as well as its receptor, neurotrophic tyrosine kinase receptor, type2 (NTRK2), are mainly expressed in human GCs and CCs (Kawamura *et al.*, 2005; Zhao *et al.*, 2019). Interestingly, BDNF could down-regulate the expression of apoptosis-related genes Caspase 9 and TNF receptor superfamily, member 6 (FAS) in oocytes, while up-regulating the expression of NTRK2, thereby inhibiting the apoptosis of oocytes and promoting their development (Zhao *et al.*, 2019). Fas system is a cell membrane glycoprotein that belongs to the tumor necrosis factor receptor family. FasL is the only natural ligand and homologous type II membrane protein in the body. Fas exists on target cells and FasL binds to it in the form of trimer, resulting in activation of the fas-related death domain (FADD). Correspondingly, FADD stimulates the self-activation of caspase 8, which is the initiator of the caspase family. Once activated, caspase 8 can activate other downstream caspase proteases. Among them, caspase-3 is the "core" protease in the FAS-mediated apoptosis signaling pathway and the final executor of apoptosis death. Therefore, we believe that the activation of the Fas-FasL-FADD-caspase-8-caspase-3 pathway may eventually lead to irreversible apoptosis of oocytes. Furthermore, the presence of superoxide dismutase (SOD) in CCs can inhibit the death of oocytes (Matos *et al.*, 2009). Another experiment revealed that oocytes prevented the death of CCs by promoting the expression of anti-apoptotic gene BCL-2 and inhibiting the expression of pro-apoptotic gene BAX (Gilchrist *et al.*, 2008). However, this effect is limited in that the incidence of apoptosis of CCs cells around the oocyte is lower than that of CCs cells outside the COCs (Hussein *et al.*, 2005). In addition, serpin peptidase inhibitor, clade E (SERPINE2), and CDC42 genes are also involved in oocyte apoptosis (Hamel *et al.*, 2008). However, some studies have shown that Serpine2 does not play a key role in the process of follicular atresia, and compensatory effect may occur after the knockout of SerpinE2 (Cao *et al.*, 2006).

Conclusion

The analysis of GCs and CCs gene expression may act as an indicator for revealing the physiological mechanism of oocyte maturation (Liu *et al.*, 2018). The prediction and evaluation of oocyte development ability could improve the efficiency of IVM technology and increase the survival rate of transplanted embryos. The fact that CCS closely surrounds the oocyte, constantly responds to the follicular environment, and plays a central role in oocyte maturation. This led different research groups to focus on CCs to look for new markers that predict oocyte competence. Indeed, CCs analysis has exclusive advantages over direct assessment of oocytes. We did this review focused on the GCs and CCs gene expression analysis and tried to figure out their intrinsic links to oocyte maturation (Tab. 1). We found that microarray technology is a useful tool for finding new candidate genes among the literature (Assou *et al.*, 2010).

This paper first classified the correlation between GCs\CCs gene expression profile and oocyte developmental potential. We also put forward a method to monitor the expression level of GCs\CCs related genes and factors under the condition of *in vitro* maturation to judge the development ability of oocytes. Additionally, an optimized

culture medium to maximize the maturation rate of oocytes is expected to be developed in the future supporting subsequent embryo development, clinical pregnancy, and live birth. Oocytes at the IVM system could be studied in a range of measures, nevertheless, many of which were invasive (Coticchio *et al*., 2015). Gene expression profile monitor of CCs is a commendable alternative method to predict the quality of oocytes *in vitro*, and it is completely non-invasive (Uyar *et al*., 2013). Under this circumstance, this review provides meritorious information for clinical IVM techniques. The study of the gene expression profile of the CCs will yield more thrilling data, which may shed light on basic theories of obstetrics and physiology, research and application of embryo engineering, and treatment of reproductive diseases related to oocyte abnormalities in the foreseeable future. Finally, more predictors need to be explored further before IVM progresses from a research technique to a treatment method.

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