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Molecular regulation mechanism of oocyte maturation in beef cattle

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Abstract: Bovine oocytes are one of the indispensable cells in cattle reproduction and have become a research hot spot in cattle reproduction in recent years. The maturation process of oocytes is mainly regulated by enzymes, hormones, cytokines, and other molecules. The factors affecting cattle oocyte maturation have been previously studied to clarify the molecular mechanisms of cattle oocyte maturation. In this review article, phospholipid protein-3-kinase/protein kinase B, mitogen-activated protein kinase/extracellular signal-regulated kinase, Janus kinase/signal transducer and activator of transcription, epidermal growth factor receptor/extracellular signal-regulated kinase, and other signaling pathways related to oocyte maturation are discussed. In addition, the molecular mechanisms of some coding genes (*JY-1, FGF-10, CDC20*, etc.) and non-coding genes (miRNA, lncRNA, and circRNA) regulating oocyte maturation have been reviewed to provide new ideas for high reproductive performance molecular breeding of high-quality cattle.

Introduction

Oocytes are mainly of primary, secondary, and mature types, which are important for the formation of new mammalian organisms (Walker and Biase, 2020). In females, oogonia proliferate and differentiate to form primary oocytes. After the first meiosis, primary oocytes form secondary oocytes and polar bodies; these secondary oocytes form oocytes and second polar bodies after the second meiosis. Finally, both polar bodies die, and the remaining cells become mature oocytes (Duncan *et al.*, 2020). However, most oocytes stagnate in the metaphase of the first meiosis before entering puberty, and only a few oocytes can resume meiosis and reach maturity. In the stagnant stage of meiosis, the chromatin in the germinal vesicle (GV) is regulated at various levels. Morphologically, the chromosomes lose their individuality and form a loose chromatin mass. The decondensed configuration of chromatin then undergoes profound rearrangements during the final stages of oocyte growth. Functionally, the discrete stages of chromatin condensation are characterized by different levels of transcriptional activity, DNA methylation, and covalent histone modifications. These changes are crucial to confer the oocyte with meiotic and developmental competencies (Luciano *et al.*, 2014). When mammalian oocytes (including cow oocytes) are removed from follicles, they have the ability to spontaneously resume meiosis, which is believed to be the result of the lack of an unidentified follicle inhibitor in domestic animals (Sirard *et al.*, 2006). The maturation of oocytes is influenced by the functional activities of surrounding hematocele or granulation cells. These cells promote the development and maturation of oocytes by regulating various hormones, proteins, metabolites, and regulatory factors (Petro *et al.*, 2012). As the basis of embryonic engineering, the maturation of oocytes is of great significance for the development of *in vitro* fertilization, transgenesis, embryo cloning, and related biotechnology. The maturation of cattle oocytes also plays a vital role in cattle reproduction (Walter *et al.*, 2020; Gennari *et al.*, 2021). Further understanding of the molecular regulation mechanism of cattle oocyte maturation can accelerate the breeding of improved cattle, aid in tapping the reproductive potential of the most productive female cattle, and provide new means and methods for cattle breeding with high reproductive performance. It further enriches the content of cattle molecular breeding and lays a foundation for developing cattle developmental biology. Thus, this article aimed to provide new ideas for improving the high reproductive performance of high-quality cattle by elucidating the action mechanism affecting the signaling pathway of oocyte maturation and molecular mechanisms of some genes regulating cattle oocyte maturation.

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Maturation of Cattle Oocytes

The development of oocytes starts in the fetal ovary, and the final growth and maturation occur in adulthood (Hunt and Hassold, 2008). Cattle oocyte maturation (nuclear maturation and cytoplasmic maturation) refers to the process that cattle oocytes acquire the ability to fertilize after growth and development changes. Cattle excrete secondary oocytes in the middle of the second meiosis (Pan and Li, 2019). Then the sperm enters the zona pellucida, the oocytes are activated and release the second polar body, and the cattle oocytes are fully mature.

Maturation of oocytes nucleus

As the first meiosis progresses half-way, the oocyte stops dividing, and the chromatin in the nucleus is highly sparse. In addition, its morphological structure is a vesicular GV. In the presence of gonadotropins, meiosis resumes, the nuclear membrane ruptures, ribosomal RNA (rRNA) synthesis ceases, the nucleolus disappears, the nucleus densifies, and the germinal vesicle breaks down (GVBD). The first polar body is expelled and stalls at mid-second meiosis (MII) (Conti and Franciosi, 2018). Of these, the expulsion of the first polar body is the most important characteristic of oocyte nuclear maturation.

Cytoplasmic maturation of oocytes

In oocyte nucleus maturation, the cytoplasm also experiences maturation changes. Oocyte cytoplasmic maturation refers to a process in which the oocyte is prepared for fertilization by dynamic changes in the distribution of organelles (e.g., mitochondria and Golgi apparatus). Cytoplasmic maturation is characterized by molecular and structural changes involving organelles, cytoskeletal reorganization, messenger RNA (mRNA), and protein storage, among which mitochondria changes can be used as a basis of cytoplasmic maturation (Kurowska *et al.*, 2020). In the cytoplasm of most immature eggs, mitochondria show a peripheral distribution with small clusters of mitochondria, which increases in number during oocyte maturation and migrates from the cytoplasmic cortex to the cytoplasmic interior to provide energy for oocyte maturation (Roth, 2018). The migration of mitochondria to high-energy consumption regions is crucial for oocyte maturation.

Major Signaling Pathways Related to Cattle Oocyte Maturation

Similar to other mammals, the maturation of cattle oocytes is a complex and dynamic process (Wen *et al.*, 2020), and some genes and signaling pathways are also involved in its maturation process. To date, several mechanisms related to the regulations of oocyte maturation in animals have been elucidated, involving phospholipid protein-3-kinase/protein kinase B (PI3K/Akt) signaling pathway (Tomek and Smiljakovic, 2005), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathway (Frodin and Gammeltoft, 1999; Conti *et al.*, 2012), Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway (Meng *et al.*, 2015), and epidermal growth factor receptor/extracellular signal-regulated kinase (EGFR/ERK) signaling pathway (Richani and Gilchrist, 2018; Pocar *et al.*, 2020). Genes and proteins related to oocyte maturation promote or inhibit oocyte maturation through the regulation of the above signaling pathways.

The phospholipid protein-3-kinase/protein kinase B signaling pathway

PI3K/AKT signaling pathway plays a crucial role in cell proliferation (Wang *et al.*, 2019), apoptosis (Zhang *et al.*, 2020), DNA repair (Chen *et al.*, 2008), and protein synthesis (Bibollet-Bahena and Almazan, 2009; Andrade *et al.*, 2017). In animal reproduction, the PI3K/Akt signaling pathway is associated with ovarian functions in mice and other mammals, such as primordial follicle recruitment, granulation proliferation, voxel lutein survival, and oocyte maturation (Adhikari and Liu, 2009; Makker *et al.*, 2014). Activation of the PI3K/AKT signaling pathway requires the involvement of the SRC homology domain-containing protein tyrosine phosphatase 2 (SHP2), while a high expression of PI3K/AKT promotes oocyte maturation (Vigneron *et al.*, 2004; Zhang *et al.*, 2016). Epidermal growth factor (EGF) and cell factor can activate SHP2. The activated SHP2 triggers the PI3K/AKT signaling cascade, allowing PI3K to produce the second messenger phosphatidylinositol 3,4,5-triphosphate (PIP3), which binds to phosphoinositide-dependent dependent kinase-1 (PDK1), prompting PDK1 to phosphorylate threonine 308 (Thr308) of Akt protein and causing Akt to be activated at the GVBD and MI (mid-meiotic) stages of oocytes (Fig. 1). Activated Akt is activated in the MI phase, stimulating the transition from MI (mid-meiotic division I) to MII and promoting oocyte maturation (Tomek and Smiljakovic, 2005). Phosphatase and tensin homolog deleted on chromosome ten (PTEN) can convert PIP3 into phosphatidylinositol diphosphate (PIP2) (McLaughlin *et al.*, 2014), thereby negatively regulating the PI3K-AKT signaling pathway and inhibiting oocyte maturation. As the major signaling pathway affecting oocyte maturation in cattle, the PI3K/AKT pathway promotes oocyte maturation mainly by facilitating the transition from oocyte MI to MII. However, the interaction mechanism between the PI3K/AKT pathway and other signaling pathways is still unclear.

The mitogen-activated protein kinase/extracellular signal-regulated kinase

MAPK/ERK signaling pathway is a protein signaling cascade pathway for oocyte maturation in mammals, such as cattle, sheep, pigs, horses, and mice (Fan and Sun, 2004). Although spontaneous GVBD of mammalian oocytes does not require MAPK activity, artificially increased MAPK activity also accelerates GVBD (Fan and Sun, 2004). In bovine oocytes, MAPK is activated by the injection of Moloney sarcoma oncogene (MOS) mRNA, accelerating the resumption of oocyte meiosis. The activation state of MAPK is determined by the balance between the upstream mitogen-activated

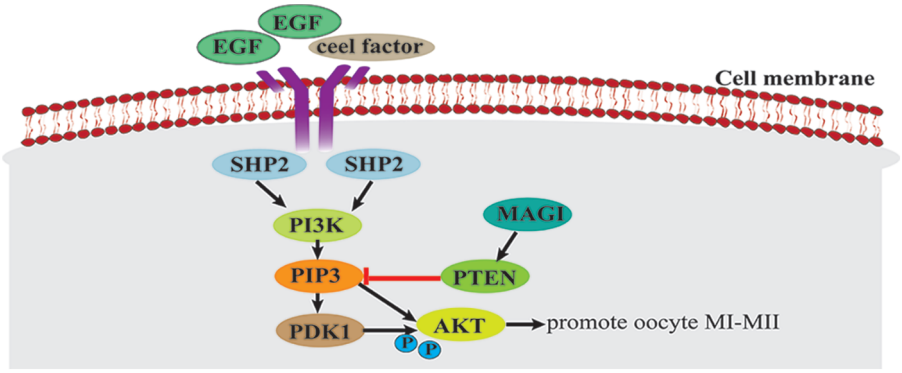

FIGURE 1. The phospholipid protein-3-kinase/protein kinase B (PI3K/AKT) signaling pathway.

extracellular signal-regulated kinase activity, the MAPK cascade activity, and the phosphatase activity responsible for the direct dephosphorylation of MAPK (Kumano *et al.*, 2001).

During oocyte maturation, ribosomal S6 protein kinase (p90RSK) activates MAPK. The activated MAPK binds to myelin transcription factor 1 protein and inactivates the C-terminal phosphorylation of MAPK, thereby promoting the phosphorylation of threonine 14 (Thr14) and tyrosine 15 (Tyr15) of cyclin-dependent kinase-1 (CDK1). It leads to the activation of the maturation-promoting factor (MPF) and enables oocytes to resume meiosis and complete the G2/M phase transformation (Frodin and Gammeltoft, 1999), promoting the maturation of oocytes.

In the granulosa cells of the preovulatory follicle, luteinizing hormone (LH) binds to its parietal granulosa cell receptor LHGC, producing cyclic adenosine monophosphate (cAMP) and activating protein kinase A (PKA). The activated PKA triggers the release of the EGF-related peptides amphiregulin (AREG) and epiregulin (EREG) release and binds to EGF receptors located on mural granulosa cells and cumulus cells (Conti *et al.*, 2012), activating ERK1/2 signaling molecules. High expression of ERK1/2 induces activation of CCAAT, enhancer-binding proteins α/β, transcriptional cofactor CITED4, and genes essential for oocyte maturation, ovulation, and luteinization and inhibits processes regulated by the follicle-stimulating hormone (FSH) pathway (e.g., estrogen synthesis, granulosa cell proliferation, etc.) (Fan *et al.*, 2008; Fan *et al.*, 2010). In addition, ERK1/2 activated by EGF family paracrine factors in cumulus cells phosphorylates connexin 37 (CX37), which reduces the transmission of cAMP and cyclic guanosine monophosphate (cGMP) molecules between cumulus cells and oocytes. In oocytes, cAMP inhibits the resumption of meiosis, and cGMP inhibits phosphodiesterase 3A (PDE3A), which is responsible for the degradation of cAMP. The reduction of cAMP and cGMP in oocytes prevents the inhibition of PKA on CDK1, and the activation of CDK1 allows oocytes to break the GV phase block and enter the division phase (Su *et al.*, 2002; Sela-Abramovich *et al.*, 2005; Fan *et al.*, 2011), promoting oocyte growth and maturation.

The MAPK/ERK signaling pathway plays a vital role in promoting follicle development and oocyte growth maturation (Fig. 2). Although the MAPK/ERK signaling pathway was studied, its specific mechanism during follicle development and oocyte maturation in cattle still needs to be further elucidated.

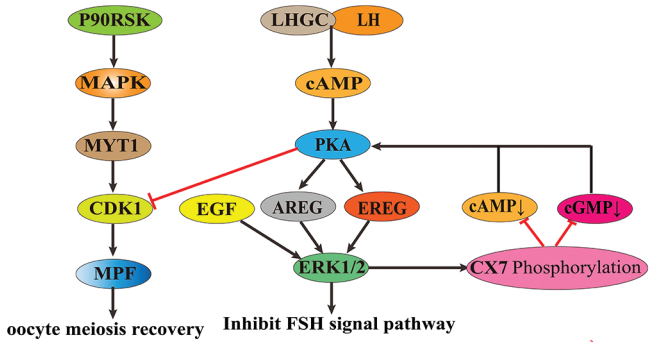

FIGURE 2. The role of mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathway in animal oocyte maturation.

The Janus kinase/signal transducer and activator of the transcription signaling pathway

The JAK/STAT3 signaling pathway has three main components: receptors, JAKs, signaling sensors, and STATs (Brooks *et al.*, 2014). JAK family is composed of non-receptor tyrosine protein kinases (TYKs), comprising four family members, JAK1, JAK2, JAK3, and TYK2. When cytokines bind to their receptors, JAK tyrosine kinases are activated and transmit regulatory signals (Hu *et al.*, 2021). The STAT family consists of STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. In organisms, STAT3 acts as a signal sensor and an activator of transcription and is activated into DNA-binding proteins through tyrosine phosphorylation (Zhong *et al.*, 1994; Hu *et al.*, 2021).

After participating in cytokine receptors, such as leukemia inhibitory factor (LIF), members of the JAK family are phosphorylated, leading to the phosphorylation of downstream STAT proteins. Phosphorylated STAT protein promotes cytoplasmic STAT dimerization and translocates to the nucleus to regulate the transcription of the prolactin gene (*PRL*) (Martínez-Alarcóna *et al.*, 2022). *PRL* promotes oocyte maturation through its receptor-mediated calcium regulation mechanism (Meng *et al.*, 2015) (Fig. 3).

The Epidermal growth factor receptor/extracellular signal-regulated kinase signaling pathway

EGFR (also known as HER1) is a member of the epidermal growth factor receptor (HER) family, which includes HER1, HER2, HER3, and HER4, and plays an important regulatory

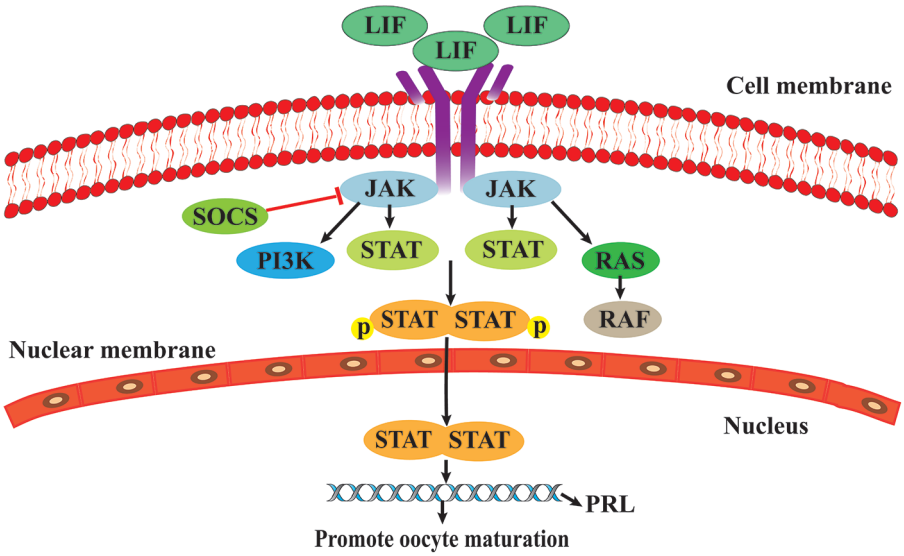

FIGURE 3. The role of Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway in oocytes maturation.

role in the regulation of cell physiology. EGFR can be activated by EGF-like peptides (e.g., heparin-binding EGF-like growth factor, transforming growth factor alpha [TGF-α], AREG, and EREG) and converted from monomers to dimers. Stimulation of the EGFR pathway initiates a phosphorylation cascade that activates ERK1/2. Activating ERK1/2 can mediate the translocation of aromatic hydrocarbon receptor (AHR) to the nucleus and form a heterodimer with the AhR nuclear translocator (ARNT) when binding to ligands. Then, the AhR/ARNT complex binds to a specific DNA sequence in the promoter of the target gene cytochrome P450 family 1 subfamily A member 1 (*CYP1A1*) and triggers its expression. *CYP1A1* affects oocyte maturation by promoting the resumption of oocyte meiosis (Pocar *et al.*, 2020) (Fig. 4). In addition, EGFR can induce the expansion of granulation sugar and hydrops cells in follicles by transmitting LH signals to oocytes (Richani and Gilchrist, 2018) and promote the maturation of the oocyte cytoplasm.

Signaling pathways, such as tumor necrosis factor, Wnt/β-catenin, TGF-β, and cAMP, are related to the maturation of cattle oocytes. TGF-β/SMAD signal transduction is caused by the TGF-β and TβRII trigger, TβRII in turn, recruits and phosphorylates TβRI. After TβRII is activated, TβRI phosphorylates R-Smad (Smad 2 or 3), binds it with a common Smad (Smad 4), forms complexes, that translocate to the nucleus, where they regulate the transcription of various target genes together with transcription factors (Hata and Chen, 2016). FSH and LH can regulate the level of natriuretic peptide precursor in mural granulosa cells through TGF-β to regulate the meiotic process of oocytes and affect the maturation of oocytes (Feng *et al.*, 1988; Yang *et al.*, 2019). In addition, TGF-β Superfamily members (such as bone morphogenetic protein 15 [BMP15] and growth and differentiation factor 9 [GDF9]) or related growth factor binding proteins (such as (*trans,trans*)-1-fluoro-2,5-bis(3-hydroxycarbonyl-4-hydroxy)styrylbenzene or FSB) have been shown to regulate bovine oocyte maturation (Zhang *et al.*, 2015).

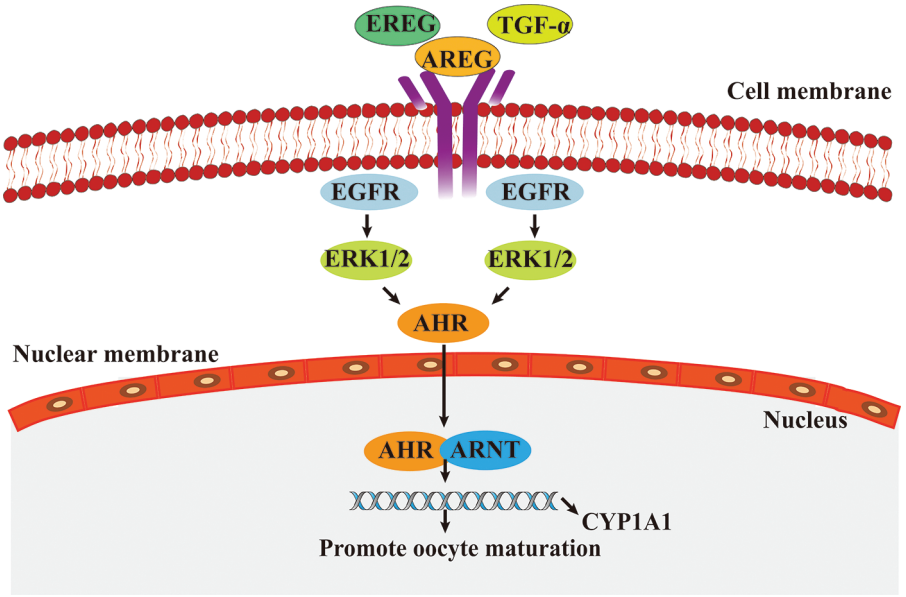

FIGURE 4. The role of epidermal growth factor receptor/extracellular signal-regulated kinase (EGFR/ERK) signaling pathway in oocytes maturation.

Molecular Regulation of Coding Genes during Maturation of Cattle Oocyte

The maturation of oocytes depends on the regulation of many factors. In addition to the environment, oocyte maturation is regulated by many genes (*JY-1, FGF-10, CDC20*, etc.). Studies suggest that oocyte-expressed *JY-1* is required for at least two important aspects of oocyte maturation: nuclear maturation and cumulus expansion (Lee *et al.*, 2014). Pocar *et al.* (2004) found that *CYP1A1* promotes oocyte maturation by activating the AHR signaling pathway and proved the physiological role of AHR in meiotic recovery. Yang *et al.* (2021) analyzed the porcine GV and MII oocytes by single-cell RNA sequencing (RNA-seq) technology and found 1807 (602 up-regulated and 1205 down-regulated) differential mRNAs, which are mostly enriched in biological and signal pathways related to the meiosis of oocytes.

The 19 coding genes reviewed in the table below regulate oocyte maturation in cattle by up-regulating or down-regulating the expression of genes in related signaling pathways (Table 1). These studies provide a theoretical basis for further exploring and revealing the basic laws of cattle reproduction. However, in the process of oocyte maturation, there are many differentially expressed genes. Further studies are needed to explore how some genes play roles through key genes and related signaling pathways.

Regulation of Non-Coding Genes on Cattle Oocyte Maturation

Non-coding genes achieve their biological functions through interactions with their target genes (Bhatt and Ferrell, 1999). Studies have shown that microRNA (miRNA) (Uhde *et al.*, 2017), long non-coding RNA (lncRNA) (Li *et al.*, 2021), and circular RNA (circRNA) (Fu *et al.*, 2018) have regulatory effects on the maturation of cattle oocytes.

Regulation of miRNA on the maturation of cattle oocytes

MiRNAs are a class of regulatory RNAs, which are short-stranded non-coding RNAs of 21–25 nucleotides in length

TABLE 1

Genes related to oocyte maturation

Gene name	Mechanism of action	Change in expression	Reference
JY-1	*JY-1* protein affects bovine oocyte maturation.	Up	Lee *et al.* (2014)
FGF10	Oocyte maturation acts as an upstream regulator of BMP15 expression.	Up	Zhang *et al.* (2010)
CDC20	Down-regulation leads to a decrease in the emission of the first polar body during oocyte maturation.	Down	Yang *et al.* (2014)
PTPN11	The coding protein SHP2 is activated by growth factors and is highly involved in oocyte maturation.	Up	Idrees *et al.* (2019)
H1FOO	Overexpression of the *H1FOO* gene promotes oocyte maturation.	Up	Yun *et al.* (2015)
PANX1	Increases the cAMP level and delay oocyte maturation by inhibiting *PANX1*.	Up	Dye *et al.* (2020)
FGF2	*FGF2* promotes meiotic recovery.	Up	Barros *et al.* (2019)
LIF	*LIF* promotes oocyte maturation by inducing miR-21 through STAT3.	Up	Vendrell-Flotats *et al.* (2020)
SIRT2	Inhibition of *SIRT2* can lead to meiotic arrest, thus inhibiting oocyte nuclear and cytoplasmic maturation.	Up	Xu *et al.* (2019)
Ghrelin	It acts on AKT1 and ERK1/2 phosphorylated oocytes and accelerates oocyte maturation.	Up	Chouzouris *et al.* (2017)
CX37 and *CX43*	Promote cellular communication between hematocele and oocyte.	Up	Sabry *et al.* (2021)
PLK4	*PLK4* knockout inhibits cytoplasmic maturation in oocytes.	Up	Liang *et al.* (2016)
APLN	The maturation of the bovine oocyte nucleus was prevented by inhibiting progesterone secretion.	Down	Roche J (2017)
CYP1A1	*CYP1A1* promotes oocyte maturation by activating the AHR signaling pathway.	Up	Pocar *et al.* (2004)
RMVGR	*RMVGR* silencing severely reduces oocyte development and egg maturation.	Down	Hussein *et al.* (2019)
AURKA	Phosphorylation of CPEB promotes the separation of oocyte chromosomes, maintains metaphase-II, and forms the first polar body.	Up	Uzbekova *et al.* (2008)
PGE2	Oocyte maturation is delayed by inhibiting *PGE2* synthesis.	Down	Marei *et al.* (2014)
MEL	Melatonin synthesis significantly promoted oocyte maturation.	Up	Tian *et al.* (2014)
EGF	Oocyte maturation is promoted by receptor EGFR.	Up	Jamnongjit *et al.* (2005)

TABLE 2

Mechanism of miRNAs on cattle oocyte maturation

MiRNA name	Target gene	Action mechanism	References
miR-21	*BMPR2* and *PTX3*	Inhibit the oocyte cytoplasmic maturation by down-regulating *BMPR2* and *PTX3* genes.	Zeinab *et al.* (2021)
miR106a	*WEE1A*	Inhibit the expression of *WEE1A* in oocytes and promote the maturation of bovine oocytes.	Miles *et al.* (2012)
miR-130b	*SMAD5* and *MSK1*	It can promote the maturation of oocytes by regulating the proliferation and metabolic activity of surrounding cells.	Sinha *et al.* (2017)
miR-494 and miR-20a	*PTEN*	Promote oocyte maturation by decreasing the expression of *PTEN*.	Andrade *et al.* (2017)
Let-7	*MYC*	Inhibit the activity of *MYC* in oocytes and promote the maturation of oocytes.	Zeinab *et al.* (2021)
miR-375	*ADAMTS1* and *PGR*	Inhibit oocyte maturation by inhibiting the expression of *DAMS1* or *PGR*.	Zhang *et al.* (2019)
miR-155	*SMAD2*	Reduce oocyte maturation by inhibiting the expression of *SMAD2*.	Dehghan *et al.* (2020)

(Turchinovich *et al.*, 2011). In mammalian cells, the seed region of miRNAs can bind complementarily to sequences on the three prime untranslated regions (3′UTR) of target genes, inhibiting the expression and translation of target genes (Turchinovich *et al.*, 2011). MiRNA levels change during oocyte maturation and ovarian follicle development in cattle, implying that miRNAs may have a regulatory role (Uhde *et al.*, 2017; Salas-Huetos *et al.*, 2019).

In the physiological process of oocyte growth and maturation, multiple miRNAs act on PI3K/Akt, JAK/STAT, and ERK/MAPK signaling pathways to promote or inhibit cattle oocyte maturation by binding to target genes, such as WEE1 homolog (Schizosaccharomyces cerevisiae) (WEE1A), MYC proto-oncogene (MYC), SMAD family member 5 (SMAD5), SMAD2, and BMP type II receptor (BMPR2), respectively (Table 2).

Regulation of lncRNA on the maturation of cattle oocytes

LncRNAs are non-coding RNAs over 200 nucleotides in length that regulate post-transcriptional base editing and translational control of mRNAs and exhibit significant biological roles by affecting the potential regulatory functions of proximity genes (Choi *et al.*, 2019). LncRNAs can participate in post-transcriptional gene regulation through processes, such as RNA maturation, transport, protein synthesis, and silencing of transcribed genes through chromosomal regulation (Whitehead *et al.*, 2009; Geisler and Coller, 2013). However, the molecular mechanism of lncRNA regulation of ovarian oocyte maturation in cattle has been less studied. Li *et al.* (2021) have identified 1761 differentially expressed lncRNAs by RNA sequencing of bovine GV and mature MII oocytes and found that the above lncRNAs may participate in the maturation of cattle oocytes from GV to MII by regulating key signal pathways. Particularly, lncRNA MSTRG17927, which is significantly decreased in MII stage oocytes, is involved in oocyte maturation through PI3K signaling (Wang *et al.*, 2020). In addition, MSTRG19140 is involved in cattle oocyte meiotic resumption, progesterone-mediated oocyte maturation, and cell cycle regulation (Li *et al.*, 2021). Notably, the MSTRG.283534.2, MSTRG.222844.7, MSTRG.77987.3, MSTRG.123289.5, and MSTRG.18894 are associated with the oocyte maturation of sheep (Shabbir *et al.*, 2021).

To summarize, the function of lncRNA in livestock oocyte maturation has been partially studied, but the functional study in cattle oocytes has just started. Further exploration of lncRNA expression in cattle oocytes and the mechanism of action on oocyte maturation are the urgent problems to be solved in the present study.

Regulation of circRNA on the maturation of cattle oocytes

In recent years, circRNA has attracted attention as a new member of the non-coding RNA family. CircRNA is a new endogenous non-coding RNA, which can regulate gene expression and various biological processes by acting as a miRNA sponge (Xie *et al.*, 2020). Hu *et al.* (2018) found that circRNAs might regulate ovarian follicle development in ewes by binding miRNAs that regulate the expression of target genes. For example, circ0008219 can regulate follicle growth in ewes by regulating miR-34c-5p, miR-483, and miR-1468-3p to prevent follicular occlusion from leading to granulocyte apoptosis (Hu *et al.*, 2018). Cao *et al.* (2019) screened 7067 and 637 circRNAs in cumulus cells and oocytes, respectively, through in-depth sequencing and bioinformatics analysis, and found that some circRNA host genes were significantly enriched in various signal pathways related to cumulus cell function and oocyte maturation. Fu *et al.* (2018) constructed four complementary DNA (cDNA) libraries of bovine cumulus cells, identified 1706 circRNAs, and screened out differential circRNA expression. Through functional annotation and enrichment analysis of host genes, differential circRNA participated in biological processes, such as movement, reproduction, biological adhesion, growth, and so on.

CircARMC4 is an up-regulated circRNA in porcine oocytes required for meiotic maturation and early

embryonic development. Inhibition of circARMC4 expression significantly reduced the expulsion of the first polar body of porcine oocytes, leading to a significant decrease in the maturation rate of porcine oocytes, which is the first demonstration of the regulatory role of circRNA on oocyte maturation (Cao *et al.*, 2019). CircRNAs may also regulate oocyte growth and maturation by regulating signaling pathways related to oocyte maturation, but their specific mechanisms of action are not yet clear. In conclusion, circRNA in the maturation of animal oocytes was preliminarily studied. However, studies on the maturation of cattle oocytes should be explored in the future.

Conclusions

As an indispensable cell in cattle reproduction, the rapid maturation of cattle oocytes is conducive to breeding high-quality cattle with high reproductive performance. In recent years, in-depth research on the signaling pathways, functional genes, and molecular markers affecting and regulating oocyte maturation in cattle has been conducted. However, the research on the application of lncRNA and circRNA in the maturation of cattle oocytes is in its initial stage. Furthermore, the molecular regulatory network participation remains to be clarified. Therefore, it is still necessary to excavate more genes related to cattle oocyte maturation in the future and clarify its mechanism through gene function research technology to provide new ideas for the molecular breeding of high reproductive performance of high-quality cattle.

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