Factors Influencing Yak Oocytes Maturation and Developmental Competence

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The yak (*Bos grunniens*) is a unique breed living on the Qinghai–Tibet Plateau and its surrounding areas, providing locals with a variety of vital means of living and production. However, the yak has poor sexual maturity and low fertility. High-quality mature oocytes are the basis of animal breeding technology. In vitro culturing of oocytes and embryo engineering technology have been applied to yak breeding.

yak oocyte in vitro maturation embryo development

1. Introduction

The yak is a unique breed that lives in the Qinghai–Tibet Plateau and offers various necessities for local people's survival and production. However, the reproductive performance of the yak is low. Yaks are generally calved every other year, with one in two years or two in three years, and the average annual reproductive rate for female yaks is less than 60% [1][2]. The yak has low reproductive performance due to various factors, including seasonal breeding, delayed puberty, and a low frequency of estrus [2][3][4][5].

In order to improve the reproductive performance of yaks, assisted reproductive procedures such as in vitro fertilization (IVF), somatic cell nuclear transfer (SCNT), and embryo transfer (ET) have been widely used in yak breeding [6][7][8][9]. These technologies cannot be implemented without high-quality mature oocytes. The process of oogenesis can be divided into three main stages: The first stage is the proliferation stage. This stage begins with the migration of primordial germ cells to the embryonic reproductive ridge that has not yet begun to differentiate. At this time, the female germ cells are called oogonia, and the oogonia carry out mitosis and proliferate continuously. In the middle and late stages of embryonic development, some oogonia begin to accumulate nutrients, grow, and undergo the first meiosis (MI). These cells are called primary oocytes. Primary oocytes go through the leptotene, zygotene, and pachytene stages, and finally arrest in the diplotene stage. The second stage is the growth stage, in which the volume of oocytes increases significantly, the number and shape of organelles changes greatly, and many nutrients, such as protein, carbohydrates, and lipid droplets are accumulated in the cytoplasm. The third stage is the maturity stage [10]. The oocyte completes its growth and approaches the size of the mature oocyte in volume. At this time, the arrested oocyte has an intact nuclear envelope known as the germinal vesicle (GV). Upon sexual maturity, primary oocytes resume meiosis by overcoming the effect of oocyte maturation inhibitors secreted by granulosa cells under the influence of luteinizing hormone (LH) peaks. After that, a series of changes, such as germinal vesicle break down (GVBD), chromosome aggregation, and uniform distribution of organelles in the cytoplasm occurs, and the primary oocyte subsequently completes the first meiosis, produces a secondary oocyte

with half the number of chromosomes, and extrudes a first polar body. Then, the oocyte arrests again in the second meiotic metaphase (MII) and waits for fertilization. Sperm penetration causes the second polar body to extrude and the formation of a diploid fertilized egg, initiating the development of the fertilized egg, cleavage, and blastocyst formation [11][12][13].

2. Endogenous Factor

2.1. Dynamic Transcripts and Protein Changes

The maturation and development of oocytes are complicated processes involving the regulation of various genes and proteins [14][15]. Dynamic changes of transcripts and proteins were observed during the development and maturation of yak oocytes [16][17]. Pei Jie et al. constructed the molecular structure of yak ovarian cortex cells using single-cell RNA sequencing (scRNA-seq). They identified the molecular features and biological functions of different cell populations. Differentially expressed genes (DEG) between oocytes and other types of ovarian cells were mainly enriched in cell cycle transition, DNA repair, and chromosome segregation processes, according to Gene Ontology (GO) enrichment analysis. Gene expression specificity testing indicated that the characterized genes *CENPF*, *TOP2A*, *MIS18BP1*, *FST*, and *INHA* were highly expressed in yak oocytes. The *FST* and *TOP2A* genes could be considered as the molecular features of yak oocytes within primordial follicles. They also discovered that the yak oocytes regulated the other types of ovarian cells primarily via the interaction between the ligands FAM3, INHA, and JAG1 with their corresponding receptors. However, the endothelial, epithelial, and granulosa cells regulated the oocytes principally via the BMP family [18].

2.2. Epigenetic Regulations

Epigenetic regulation is a kind of regulation of gene expression by changing non-gene sequence, mainly including DNA methylation, histone modification (acetylation, methylation, phosphorylation, etc.), and regulation of non-coding RNA, etc., which is a hot research topic in different fields of biology [19][20].

2.3. G Protein-Coupled Receptor 50 (GPR50)

GPR50 is an orphan G protein-coupled receptor on the X chromosome [21]. Previous research revealed that GPR50 was strongly expressed in yak brain, ovary, and testis tissues, implying that GPR50 might have a function in reproductive development [22]. Yao Ying et al. found that the GPR50 protein was centrally expressed in the membrane during the germinal vesicle (GV) phase of yak oocytes, with the highest GPR50 expression level during the MII phase [22]. Based on these observations, researchers investigated the impacts of *GPR50* knockdown and overexpression on yak oocytes. The results indicated that the *GPR50* knockdown significantly reduced the oocyte maturation rate and the polarbody excretion rate, while *GPR50* overexpression exerted no significant influence on the excretion rate and maturity level of the yak oocytes, suggesting that GPR50 might play a crucial role in yak oocyte maturation in vitro [23].

3. Exogenous Factor

3.1. Growth Factor

Growth factors are a class of peptides that regulate multiple effects, such as cell growth and other cellular functions, by binding to specific, high-affinity cell membrane receptors. They play critical roles in resuming oocyte meiosis, oocyte maturation, and follicular development [24][25]. Moreover, growth factors can significantly improve the development ability of embryos and promote blastocyst formation, which has great biological effects on the development processes and different developmental periods of mammalian embryos [26][27][28].

Several important growth factors, such as epidermal growth factor (EGF), insulin-like growth factor I (IGF-1), fibroblast growth factor 10 (FGF10), and leukemia inhibitory factor (LIF) are essential for oocyte maturation and embryo development. EGF can promote cell proliferation, differentiation, and mammalian oocyte maturation [24][29][30][31]. Ma Li et al. discovered that supplementation with 40 μg/mL EGF could significantly improve oocyte maturation and the development ability of parthenogenetic embryos [32]. Pan Yangyang, et al. found that the medium supplemented with 100 ng/mL EGF could significantly increase the yak COC maturation rate, and cleavage and blastocyst rates after fertilization. This might be caused by the inhibition of EGF on the expression of the pro-apoptosis gene *BAX* and the promotion of EGF on the expression of anti-apoptosis genes *BI-1* [33].

IGF-1 belongs to the insulin-like growth factor family [34], which is involved in mediating cellular proliferation, differentiation, and apoptosis, and plays a critical role in mammals' growth and development [35]. Pan Yangyang et al. discovered that adding 100 ng/mL IGF-1 to the culture medium significantly increased the yak oocyte maturation rate in vitro and the cleavage and blastocyst rates of chemically activated embryos. Further study proved that this result was due to the up-regulation of IGF-1-induced cold-inducible RNA-binding protein (CIRP) [36].

FGF10 is a paracrine fibroblast growth factor involved in numerous biological processes, including embryonic development, cell growth, morphogenesis, tissue repair, tumor growth, and invasion [37][38][39][40]. It is also involved in follicle development and oocyte maturation in various mammals [41][42]. Pan Yangyang et al. found that adding 5 ng/mL of FGF10 to the culture medium of yak COCs improved the yak oocyte maturation rate and fertilization ability. This positive effect was achieved via the up-regulation of FGF10 on *CD9*, *CD81*, *DNMT1* and *DNMT3B* expressions in COCs to optimize sperm–egg interaction and DNA methylation during fertilization [6].

LIF is a potent cytokine in the IL-6 family of cytokines [43]. Zhao Tian et al. indicated that adding LIF during the IVM of yak oocytes improved oocyte quality, maturation competence, blastocyst quality, and oocyte development. The addition of LIF (50 ng/mL) to the maturation medium could increase the maturation rate and significantly lower ROS generation and the apoptosis levels of oocytes by increasing the mRNA transcription levels of anti-apoptotic and antioxidant-related genes *BCL2*, *CAPASE3*, *SURVIVIN*, *SOD2* and *GPX4* in yak oocytes. Furthermore, blastocysts formed from 50 ng/mL LIF-treated oocytes had higher total cell numbers and lower apoptosis rates than the control group [44].

3.2. Antioxidants

ROS are small molecules produced by biological aerobic metabolism, an include superoxide, peroxide, and oxygen radicals [45]. Reactive oxygen molecules are chemically reactive due to extra-nuclear unpaired electrons. Excessive ROS attack intracellular small molecules, such as lipids, proteins, and nucleic acids, leading to DNA degradation in the nucleus and mitochondria, causing intracellular protein denaturation, inactivating some important enzymes, inducing cellular plasma peroxidation, and ultimately triggering cell apoptosis [46]. High ROS levels accelerated the oocyte senescence, reduced oocyte quality, and caused oocyte apoptosis [47][48].

Vitamin A is an indispensable nutrient that regulates physiological processes such as reproduction, embryonic development, vision, growth, cell differentiation, and proliferation [49]. Vitamin A can be oxidized to retinoic acid (RA) via oxidation reactions, and RA functions as a gene expression regulator [50]. Vitamin A regulates oocyte maturation via typical and atypical signaling pathways [51][52]. According to studies, adding 2 μM Vitamin A to yak oocytes in vitro maturation medium significantly increased the rate of IVM and parthenogenetic activation (PA) embryo cleavage rate. The expressions of *STRA8*, *RARA*, and *RXRA* were highest in the MII stage compared with those in the GV and MI stages under the treatment of 2 μM Vitamin A. Additionally, the mRNA expressions of several genes in the typical signaling pathway, including *RXRA*, *RARA*, and *STRA8*, were significantly higher than those of *MEK* and *MEK1*, which were node genes of the atypical signaling pathway. These results suggested that RA was mainly dependent on the typical signaling pathway for the yak oocyte development in vitro [53][54].

Vitamin C (ascorbic acid) is a strong water-soluble antioxidant that can catalyze the reduction of oxidized glutathione to reduced glutathione [55]. Exposure of yak oocytes to 1 nM Aflatoxin B1 (AFB1) induced early oocyte apoptosis and increased intracellular ROS levels. It caused incomplete actin and uneven distribution of mitochondria, resulting in decreased quality of mature yak oocytes. However, adding 50 μg/mL Vitamin C to the culture medium protected yak oocytes from the toxic effects of AFB1 exposure. Specifically, 50 μg/mL Vitamin C reduced intra-oocyte ROS levels, repressed early oocyte apoptosis, improved mitochondrial distribution status, and restored actin distribution [56][57].

The addition of antioxidants to oocytes and embryos during in vitro culture is necessary to maintain normal levels of intracellular ROS. Melatonin is a natural endogenous indole hormone produced by the mammalian pineal gland [58]. Since melatonin is fat- and water-soluble, it can easily transfer hydrogen and electrons across cell membranes, directly scavenging free radicals and reducing cellular ROS levels [46]. Peng Wei et al. investigated the effects of melatonin on the IVM of yak oocytes by adding different concentrations of melatonin to the culture medium of yak COCs. They discovered that adding 10^{-9} M melatonin could significantly increase the oocyte maturation rate, IVF embryo cleavage and blastocysts rates, and GSH content of oocytes and blastocysts. Reductions of ROS levels, mitochondrial protein extent, DNA damage, and cell apoptosis were observed after melatonin treatment. Additionally, 10^{-9} M melatonin repaired the spindle mismatch and chromosomal abnormalities caused by oxidative stress. The results suggested that 10^{-9} M melatonin addition could alleviate oxidative stress during the IVM of oocytes and improve the oocyte maturation rate and the developmental ability of subsequent embryos [59][60].

3.3. Microelement

Zinc (Zn) is an essential trace element in mammals that plays an important role in cell growth, proliferation, division, and immunity [61][62]. Xiong Xianrong et al. discovered that adding 2 mg/L zinc sulfate to the IVM medium of yak oocytes increased glutathione (GSH) content, superoxide dismutase (SOD) activity, and the blastocyst rate, and significantly reduced ROS levels. This effect could be achieved by Zn^{2+} inducing the up-regulation of *Zn transporters 3* (*ZnT3)*, *Zrt*, and *Irt-like protein 14* (*ZiP14*) expressions in yak oocytes [63]. Hu Jiajia et al. obtained similar results in their study. Moreover, they discovered that adding 2 mg/L zinc sulfate significantly increased the expression levels of *Solute-linked carrier* (*SLC30A*) and *SLC39A* family members, including *SCL30A3*, *SLC30A6*, *SCL30A9*, *SLC39A6* and *SLC39A14* in yak mature oocytes, facilitating the cleavage of the fertilized ovum and blastocyst formation [64]. Feng Yun et al. revealed that adding 0.8 mg/L zinc sulfate could improve the yak oocyte maturation and the efficiency of in vitro fertilization by increasing the antioxidant enzyme gene (*SOD1*, *CAT*, *TXN1*, and *PRD1*) expression levels, and also up-regulating the cumulus cell expansion related genes (*PTX3* and *TSG6*) in the oocyte [65].

Calcium (Ca) is an important second messenger in cells, and the changes in Ca^{2+} concentration are closely related to regulating physiological functions by affecting signal transduction [66]. Chen demonstrated that adding Ca^{2+} at 0.24 mM in yak oocyte culture medium significantly increased the oocyte maturation rate in vitro. The mechanism was that Ca^{2+} activated the activity of calmodulin-dependent protein kinaseII (CaMKII), increased GSH content, and decreased the ROS level in the oocyte. Ca^{2+} up-regulated the expressions of *BCL-2*, *EGF*, *EGFR*, and *C-FOS*, whereas it down-regulated *BAX* expression [67].

Selenium (Se) is an essential trace element for reproduction, immunity, antioxidant systems, embryonic growth, and other physiological functions [68][69][70]. Xiong Xianrong et al. observed that 2 μg/mL of sodium selenite significantly increased the glutathione peroxidase (GSH-Px) activity in the oocytes and the blastocyst rate of subsequent embryos by adding sodium selenite to the in vitro culture medium of yak COCs. Those effects were achieved by increasing the selenoprotein synthesis-related gene expression levels, including *GPX4*, *SEPP1*, *RPL22*, and *CCND1* in oocytes and cumulus cells [71].

3.4. Small Molecule Compounds

Cyclic adenosine monophosphate (cAMP) is the first discovered second messenger. cAMP can regulate the various target genes' transcription, primarily via protein kinase A (PKA) and its downstream effectors [72]. cAMP plays a key role in maintaining oocyte meiotic arrest and initiating meiotic resumption in mammalian oocytes [73][74]. Previous studies have demonstrated that maintaining cAMP levels in oocytes before oocyte maturation could temporarily repress spontaneous meiotic resumption, thereby improving oocyte developmental competence and subsequent embryonic development [75][76][77][78]. Xiong Xianrong et al. revealed that a supplement with a cAMP activator, cilostazol, would benefit yak oocytes IVM by increasing cAMP and GSH levels and modulating mRNA expression patterns during pre-IVM. Specifically, adding cilostazol to the in vitro maturation medium and pre-IVM for 2 h or 4 h significantly increased the *PKA1* and *CY3* mRNA expression levels. It also significantly decreased the *PDE3A* mRNA expression level in yak COCs and blastocysts [79].

Roscovitine and C-type natriuretic peptide (CNP) are two meiotic arrest factors promoting yak oocyte maturation in vitro. Roscovitine is a member of the 2,6,9-trisubstituted purine family and has a structure similar to ATP. Therefore, roscovitine interacts with amino acids in the ATP-binding pocket of the catalytic domain of some Cyclin-dependent kinases (CDK), preventing ATP from binding to CDK, inhibiting CDK activity, and ultimately blocking the cell cycle [80]. Pretreatment of yak COCs with 12.5 μM roscovitine for 6 h followed by conventional IVM improved the quality of yak mature oocytes. Liu Yu counted the cell expansion index (CEI) of ovarian thalamus granulosa cells after treating pre-IVM yak COCs with different concentrations of roscovitine. They discovered that pretreatment with 12.5 μM roscovitine for 6 h significantly increased the CEI of COCs. This treatment significantly reduced the ROS content in oocytes, promoted the uniform distribution of mitochondria, and enhanced the structure of transzonal projections (TZPs), thereby improving the quality of yak oocytes. Furthermore, this treatment significantly up-regulated the mRNA expressions of antioxidant gene *SOD2*, anti-apoptotic gene *BCL-2*, and development-related genes *GDF9*, *EGFR*, and *ZAR1*, and significantly down-regulated the mRNA expression of the pro-apoptotic gene *BAX* [81].

CNP is a natural determinant of meiotic arrest that can maintain gap junction activity and support the key gene expressions essential for oocyte development [82]. Jing Tian counted the number of yak GV oocytes cultured with different concentrations of CNP and discovered that the quality, maturation rate, and blastocyst rate of yak oocytes could be significantly improved by pre-IVM of oocytes at 100 nM CNP for 6 h and IVM for 28 h. This treatment significantly increased TZP and GSH protein expressions and decreased ROS levels in yak oocytes. These effects might be due to CNP significantly promoting the expressions of CNP receptor gene *NPR2*, anti-apoptotic gene *BCL-2*, and growth differentiation factor *GDF9* in oocytes and blastocysts. CNP suppressed the *EGF* and its receptor *EGFR* gene expressions in oocytes while promoting *EGF*, *EGFR*, and *DNMT1* expressions in blastocysts and repressing the expression of pro-apoptotic gene *BAX* in blastocysts [83].

3.5. Hormones

Xiao Xiao et al. demonstrated that supplementing IVM medium with 5 μg/mL FSH and 50 IU/mL LH improved the developmental ability of yak oocytes after in vitro fertilization (IVF) [84]. He Honghong et al. studied the effects of different concentrations of FSH concentrations on yak oocytes and revealed that the oocyte maturation rate was highest in the 5 μg/mL FSH treatment group. Further study indicated that FSH might improve yak oocyte development by increasing *EGF* and *EGFR* mRNA expression levels, and it might inhibit oocyte apoptosis by increasing antiapoptotic gene *BCL-2* expression while reducing pro-apoptotic gene *BAX* expression [85].

Estradiol (E2) is the most active and predominant maternal estrogen during pregnancy [86]. A supplement of exogenous E2 or promoting endogenous E2 synthesis and secretion can improve oocyte maturation and increase cumulus cell spread during oocyte maturation in various animals [87][88][89][90][91]. Pan Yangyang et al. discovered that adding 10^{-4} mM endogenous 17β-estradiol to the IVM medium of COCs could increase the cumulus expansion and subsequent oocyte development. These might result from increasing the expressions of cumulus-expansion-related factors (*HAS2*, *PTGS2*, and *PTX3*) and the oocyte-secreted factors (*GDF9*, *FGF10*, and *BMP15*) [92].

Rfamide-related peptides 3 (RFRP-3), a structural and functional homolog of gonadotropin-inhibiting hormone (GnIH), has been proposed as a new breeding inhibitory neurohormonal peptide that plays a crucial role in the reproductive axis across various species [93][94].

Cytochrome P450arom (CYP19A1) is the key enzyme for gonadal hormone synthesis in most animals [95]. CYP19A1 up-regulated the endogenous E2 level and enhanced the developmental ability of yak oocytes. Specifically, the treatment of CYP19A1 activator AFB1 up-regulated the endogenous E2 level and increased the rates of IVM and blastocysts, while decreasing the E2 level. IVM and blastocyst rates were observed in the CYP19A1 inhibitor BPA treatment group, which implied that CYP19A1 played an essential role in oocyte and embryo development of yaks [96].

3.6. Platelet-Activating Factor (PAF)

PAF is an acetylated glycerol signaling phospholipid important physiological regulator in reproduction [97]. PAF exerts its actions via activating specific PAF receptors (PAF-R) in cells and tissues of the female reproductive tract [98]. Wang Qin explored the role of PAF in the maturation of yak oocytes and early embryonic development by adding different concentrations of PAF to the maturation medium of COCs in vitro. The results showed that 10^{-7} mol/L PFA significantly increased the maturation, cleavage, and blastocyst rates of yak oocytes by regulating *BAX*, *BCL-2*, *EGF*, *EGFR*, *C-FOS*, *OCT-4*, and *NANOG* gene expressions [99][100].

4. Environment Factor

4.1. Temperature

Pang Bo et al. investigated the effects of ovarian preservation temperature and the culture methods on the maturation rate of yak oocytes in vitro, and the results showed that preserving the ovaries from 20 °C to 25 °C could improve the oocyte maturation rate in vitro [101]. Ma Li et al. preserved fresh yak ovaries in saline at different temperatures (15–20 °C; 25–30 °C; 35–40 °C). The results indicated that 25–30 °C was the optimal temperature for the ovarian transport of yaks. The maturation rate of oocytes, eight-cell embryo formation, and blastocyst rates of IVM and parthenogenetic activation (PA) embryos were significantly higher than those of other groups within this temperature range [102].

4.2. Oxygen

Oxygen (O_2) is vital to maintain and complete oocyte maturation and embryonic development. Changes in oxygen concentration during oocyte maturation in vitro affect nuclear DNA methylation, intracellular reactive oxygen species (ROS) levels, and cellular aging [47][103]. Low oxygen levels are the naturally preferred microenvironment for most processes during early development and mainly drive proliferation [104][105]. Several studies proved that culturing oocytes and embryos under low oxygen conditions improved their developmental capacity [106][107][108].

Li Ruizhe compared the expression differences in the transcriptome of yak oocytes at 5% and 20% oxygen concentrations and revealed that the genes up-regulated in the 5% group were mainly involved in hypoxia response, the cell cycle, chromatin conformation and remodeling, and the cytoskeleton, including the *WDR26*, *MKP2K1*, *MAPK1*, *TICRR*, *WAC*, *EIF4ENIF1*, *ODC1*, *CHAMP1*, *MKI67*, *MCM10*, *SFMBT1*, *PBRM1*, *KAT8*, *IQGAP2*, *EPS8*, and *RANBP9* genes. The genes up-regulated in the 20% oxygen concentration group, including *ACAT1*, *ATP5MF*, *AURKAIP1*, *COX6A1*, *NDUFA10*, *NDUFA11*, *NDUFS7*, *LYRM7*, *UQCR10*, *EIF1AX*, *RPL13*, *RPL13A*, *RPL34*, *RPLP2*, *GSTA2*, *QARS*, *NOSTRIN*, *SH3BGRL3*, *TIMP1*, *S100A11*, and *PTX3*, were primarily involved in energy metabolism, protein synthesis, redox homeostasis, and oocyte regulation [109]. Additionally, Li Ruizhe et al. discovered that 5% O_2 increased the oocyte maturation rate and GSH content, decreased the oocyte ROS level, and improved the quality of PA and IVF blastocysts. The effects were achieved by decreasing the expressions of the antioxidant genes *CAT* and *GPX1*, increasing the expression of the metabolism-related gene *LDHA*, and embryo development-related genes *CDX2* and *OCT4* in yak IVF blastocysts [109][110].

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