

Influence of Long Non-Coding RNAs on Human Oocyte Development

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Abstract: Recent research findings have highlighted the pivotal roles played by lncRNAs in both normal human development and disease pathogenesis. LncRNAs are expressed in oocytes and early embryos, and their expression levels change dynamically once the embryonic genome is activated during early human embryonic development. Abnormal expression of lncRNAs was found in follicular fluid, granulosa cells and oocytes of patients, and these lncRNAs were related to cell proliferation and apoptosis, nuclear maturation and follicle development. The expression levels of some lncRNAs in cumulus cells demonstrate correlations with the quality of oocytes and early embryos. This paper aims to present a comprehensive overview of the influence of lncRNAs on the developmental process of human oocytes as well as their involvement in certain infertility-related diseases.

Keywords: cumulus cells, female infertility, lncRNA, oocyte

Introduction

Non-coding RNAs (ncRNAs) have long been regarded as transcriptional noise due to their lack of biological function. Nevertheless, mounting evidence supports the notion that long non-coding RNAs (lncRNAs) exhibit a diverse array of biological functions and participate extensively in RNA epigenetic regulation. These molecules have been identified as significant players in both normal human development and disease processes.

LncRNAs can regulate signaling pathways or interact with miRNAs and mRNAs to regulate oocyte development and maturation. By influencing ovarian granulosa cell (GC) function, certain lncRNAs actively participate in physiological conditions and pathological processes associated with ovum development such as human oocyte maturation, fertilization, embryonic development, tumorigenesis,¹ and premature ovarian failure.^{2,3} In this paper, we review the research on the influence of lncRNAs on the development of human oocyte.

Development of Oocytes

Oocytes are the largest cells in the body, and the complex process of oocyte development is called oogenesis. This complex process involves numerous interactions between the oocyte and surrounding granulosa and cumulus cells. The four stages of follicle development are: original follicle, primary follicle, secondary follicle, and mature follicle, which span over a period of several months. During the early phases of follicular development, the oocyte undergoes enlargement, and granulosa and cumulus cells (GCs) begin to surround the oocyte. As cytoplasmic content increases within oocytes during this phase, proliferation and differentiation of GCs drive formation of sinus cavities within initial follicles. Follicle-stimulating hormone (FSH) stimulates the development of these structures from early-stage sinus to pre-ovulation stage.

With the formation of the follicular antrum, the GCs gradually differentiate into two different types: mural GCs (MGCs), which are distributed around the follicular antrum, and cumulus cells (CCs), which directly envelop the oocyte. MGCs predominantly perform ovarian secretory hormone/cytokine functions while regulating oocyte development through autocrine/paracrine mechanisms. In addition to oocytes, granulosa cells are the most important type of cells in

the follicle. There is extensive communication between GCs and oocytes, and they work together as a single functional unit. The secretory function of GCs can be influenced by apoptosis or a decline in quality, subsequently affecting oocyte development and the quality of subsequent embryos.⁴ In addition, maturation signaling for oocyte meiosis is accomplished through oocyte-granule intercellular junctions.^{5,6}

The expression of GC genes has also been linked in numerous studies to different therapeutic outcomes such as oocyte maturation, fertilization, embryo development, implantation, and pregnancy.^{7–9} The transcriptomes of GCs have also been investigated to determine gamete quality¹⁰ and to explore the possibility of clinical application for infertility treatment.¹¹ LncRNAs in GCs play a significant role in normal folliculogenesis, but they also alter in function and expression in response to pathological situations. Therefore, GCs can be selected as a noninvasive indicator of oocyte competence and ovarian function.

LncRNA

ncRNAs can be divided into two main categories based on their length: small ncRNAs (less than 200 nucleotides; such as microRNA, piRNA, and snoRNA) and lncRNAs (more than 200 nucleotides). Through polyadenylation and RNA polymerase II catalysis, lncRNAs carry out a variety of biological tasks in both the nucleus and cytoplasm.^{12,13} LncRNAs are a category of non-protein-coding RNA molecules that modulate the expression of target genes at both transcriptional and post-transcriptional levels. Many lncRNAs modulate the chromatin state by recruiting chromatin-modifying enzyme proteins to specific locations in genes.¹⁴ By employing cis-regulation mechanisms that target specific genes, lncRNAs also impact the transcription and expression of genes located in close proximity. They also function as co-regulators to modulate transcription factor activity. Numerous studies have demonstrated interactions between various types of RNA molecules, such as lncRNAs and miRNAs, miRNAs and mRNAs, and lncRNAs and mRNAs.¹⁵ The interactions among these molecules collectively create a dynamic regulatory network. They bind to microRNAs (miRNAs) to modulate the expression of messenger RNAs (mRNAs), consequently diminishing the miRNAs' capacity to bind to mRNA targets.^{16,17}

LncRNAs have been discovered in a stable form in many tissues and body fluids,^{18–20} and are widely involved in the regulation of gene expression networks, such as chromosome imprinting, cell growth, and tumorigenesis.^{21–24} Research has shown that lncRNAs are expressed in oocytes and early embryos. Moreover, as the embryonic genome becomes active during the initial stages of human embryonic development, the expression levels of these lncRNAs undergo dynamic alterations.^{25,26} LncRNAs are involved in various biological and developmental processes during early embryonic development. They are involved in the induction and maintenance of cell pluripotency, X chromosome inactivation, and gene imprinting.²⁷ In the regulatory process, several lncRNAs, including Xist, Tsix, and Xite, ensure the dosage regulation of X-expressed genes.^{28,29} The expression levels of some lncRNAs in GCs are linked to the quality of oocytes and early embryos, and may play a variety of roles in early embryonic development. Consequently, these lncRNAs have the potential to serve as biomarkers for non-invasive prediction of oocyte development.

LncRNAs and Oocytes

The lncRNA profiles of MII oocytes were found to differ significantly from those of GCs, with a higher abundance of lncRNAs observed in GCs compared to MII oocytes. Additionally, in both MII oocytes and GCs, the expression levels of most lncRNAs were notably lower than those of protein-coding genes.³⁰ Some lncRNAs were found in human follicular fluid, and were most correlated with serum androstenedione levels and LH levels.³¹ The number of lncRNAs expressed in follicles gradually increases from the primitive stage to the preovulation stage, and lncRNA demonstrates stronger cell type selectivity than protein-coding genes during follicle development.³² These indicated that lncRNAs are involved in the regulation of human follicular development and are essential for the growth of oocytes. Four lncRNAs were found to be differentially expressed in mature and immature follicles of healthy women.³¹ LncRNA sequencing was performed on the mixed RNA of oocytes from each group of recurrent oocyte maturation arrest (ROMA), GV, metaphase I (MI), and MII. LncRNAs undergo a considerable alteration as oocytes develop from GV to MII stage. According to a study, NEAT1 and NORAD may inhibit oocyte maturation by regulating the expression of PRKCA and JAK3 through the PI3K-Akt pathway.³³ These findings implied that altered expression of lncRNAs may disrupt the normal process of

oocyte maturation and lead to oocyte maturation arrest. The expression of lncRNAs XISTOIP5-AS1, RN7SK, and RN7SL2 was detected in oocyte and follicle samples taken from women who had cryopreserved their ovarian tissue before chemotherapy. The expression of lncRNA GAS5 was high in primordial follicles and slightly lower in primary follicles.³⁴ In follicles, 91 lncRNAs were found to be involved in 210 dynamic sub-pathways, whereas in GCs, 17 lncRNAs were found to be involved in 234 dynamic sub-pathways.³² These findings suggest that lncRNAs may play a role in oocyte development.

LncRNAs and GCs

Yerushalmi et al discovered 1746 differentially expressed genes between compact and extended GCs.³⁵ In the GCs of both germinal vesicle (GV) and metaphase II (MII) oocytes, researchers identified 89 lncRNAs displaying differential expression. Among them, 12 lncRNAs were encoded in genes associated with GC development, and their participation in the functional regulation of GCs. The lncRNA HAS2 antisense RNA1 (HAS2-AS1) is differently expressed in the GCs of immature and mature oocytes. Inhibition of HAS2-AS1 inhibits HAS2 expression and GC migration.³⁶ To sum up, lncRNAs may regulate cumulus expansion and oocyte maturation.

Xu et al analyzed the expression pattern of lncRNAs in GCs that developed into embryos of different quality. Compared to the high-quality embryo group, 124 lncRNAs were continuously up-regulated and 509 lncRNAs were continuously down-regulated in the low-quality embryo group.³⁷ The expression levels of AK124742 and PSMD6 were increased in the high-quality group when compared to the low-quality group, and in the pregnant group when compared to the non-pregnant group. New lncRNA-messenger RNA gene pairs in human GCs, AK124742 and PSMD6, show potential interactions between lncRNAs and neighboring coding genes.³ These results suggest that the expression level of lncRNA in GC is closely related to embryo quality, and the detection of lncRNA expression in GC can predict embryo development.

Li et al analyzed the expression levels of lncRNAs in GCs of elderly and young women. A total of 28 down-regulated lncRNAs were identified in the GCs of the elderly group. Certain target genes regulated by follicle-stimulating hormone (FSH), luteinizing hormone (LH)/human chorionic gonadotropin (hCG), or other hormones interacting with these lncRNAs were expressed in GCs, playing a role in the regulation of follicle formation.³⁸ With increasing age, the expression of lncRNA changes significantly. Apopa1-AS, IGF2BP2-AS1, and PSMB8-AS1 were the most commonly down-regulated lncRNAs that were age-related and connected to angiogenesis, lipid transport, cell cycle regulation and transcriptional control.³⁹ Several lncRNAs involved in the control of oocyte maturation and follicular development processes were under expressed in GCs of women aged over 40 years old. The decreased quality of oocytes during reproductive aging may be explained by changes in protein expression associated with follicular development brought on by the downregulation of certain lncRNAs in GCs among aged patients.

Down-regulation of lncRNA HCP5 in KGN cells inhibits cell proliferation by preventing cell cycle progression in G1 phase, and induces cell apoptosis by activating mitochondrial pathway, which is achieved by regulating miR-27a-3p/IGF-1 axis.⁴⁰ In KGN cells, over expression of lncRNA GAS5 led to the up-regulation of IL-6 and significantly reduced the apoptosis rate.⁴¹ Through the P21/p53-dependent control of the cell cycle, which is mediated by the ERK/MAPK pathway, MALAT1 may regulate the proliferation of GCs.⁴² lncRNAs in GCs may directly or indirectly affect apoptosis and proliferation, and then regulate oocyte development and maturation.

These findings imply that lncRNAs in GCs may directly regulate oocyte development, or may interact with miRNAs and mRNAs to regulate oocyte maturation and embryonic development, both of which are essential for oocyte growth.

LncRNAs and Female Infertility

LncRNAs and Polycystic Ovarian Syndrome (PCOS)

In patients with PCOS, the transcription level of lncRNA PWRN2 was significantly lower in the GCs of mature oocytes in comparison with immature oocytes.⁴³ Knocking out PWRN2 in KGN cells resulted in up-regulation of 118 lncRNAs and down-regulation of 58 lncRNAs. The results of the gene ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis revealed that PWRN2-regulated genes are engaged in a variety of metabolic

processes. Several studies have identified specific lncRNAs that are up-regulated in the GCs of patients with PCOS. These lncRNAs have been found to regulate miRNAs, thereby influencing cellular development processes (Table 1).^{43–52} In individuals with PCOS, whether presenting with or without hyperandrogenism, the expression of lncRNAs exhibited significant alterations when compared to the normal control group. Notably, among these changes, lncRNA CRHBP displayed the most pronounced alteration in expression. The GO and KEGG pathway analysis revealed that CRHBP plays a crucial role in mitochondrial function by interacting with transcription factors YY1 and SIX5.⁵³ Few individual lncRNAs have been identified in the GCs of patients with PCOS, most of which are involved in the proliferation and apoptosis of GCs (Table 2).^{54–60} It can be seen that the dysfunction of lncRNAs may be related to abnormal follicles and hyperandrogen.

In patients with PCOS, the expression of lncRNA MALAT1 is reduced. Studies have confirmed that MALAT1 inhibits TGF β signaling and causes cell cycle disruption by acting as a competitive endogenous RNA (ceRNA) and interacting with miR-125b and miR-203a.⁶¹ Li et al also discovered that MALAT1 was down-regulated in GCs of patients with PCOS. MALAT1 bound to MDM2 and inhibited ubiquitination and degradation of p53, thereby increasing

Table 1 Up-Regulated lncRNAs That Regulate miRNA in GCs of Patients with PCOS

lncRNA	Regulated miRNA	Functions	Reference
PWRN2	miR-92b-3p	Influence oocyte nuclear maturation in PCOS	[43]
PVT1	miR-17-5p	Regulate the proliferation and the apoptosis of GCs	[44]
ZFAS1	miR-129	Prevent the degradation of HMGB1 and affect the endocrine disorder, proliferation and apoptosis of GCs	[45]
NEAT1	miR-16, miR-483 and miR-324-3p	Promote cell proliferation and inhibit cell apoptosis	[46]
HOTAIRM1	miR-433-5p	Promote PIK3CD expression, thereby regulating the growth and apoptosis of GCs	[47]
PLAC2	miR-19a	Participate in the occurrence of PCOS	[48]
XIST	miR-30c-5p	Inhibit cell proliferation and inducing apoptosis, and is associated with adverse pregnancy outcomes.	[49]
H19	miR-19b	Regulate the proliferation and apoptosis of GCs	[50,51]
CDKN2B-ASI	miR-181a	Affect the proliferation of GCs	[52]

Table 2 lncRNAs in GCs of Patients with PCOS

lncRNA	Up/Down regulation	Functions	Reference
HCG26	Up	Affect cell proliferation and cell cycle progression along with increased aromatase gene (CYP19A1) expression and estradiol production	[54]
BANCR	Up	Promote the expression of pro-apoptotic markers Bax and P53 to inhibit cell proliferation and induce cell apoptosis	[55]
HUPCOS	Up	Induce the excess of androgens in follicular fluid in PCOS patients	[56]
TUG1	Up	Inhibit apoptosis and autophagy of GCs by ERK/MAPK pathway, thus leading to antral follicle increase	[57]
HAS2-ASI	Up	Induce the hypermethylation in the promoter region of TGFBR2 to inhibit TGF- β signaling	[58]
MAP3K13-7:1	Up	Resulted in cell cycle arrest at G0 / G1 phase and inhibit GCs proliferation	[59]
OCI	Up	Affect the cell viability, apoptosis and production of estradiol	[60]

p53 protein levels. Knockdown of MALAT1 could increase apoptosis and decrease proliferation in KGN and primary GCs.⁶² Contrarily, Tu et al reached a distinct conclusion, observing the up-regulation of MALAT1 in GCs from patients with PCOS. Additionally, they noted the up-regulation of both MALAT1 and phosphorylated SMAD 1/5 (Ser463/465) proteins following anti-Müllerian hormone (AMH) stimulation of KGN cells. Inhibition of MALAT1 can promote the proliferation of KGN cells in vitro.⁶³ In summary, based on these studies, it is evident that lncRNAs play significant roles in regulating cell proliferation and apoptosis in GCs of patients with PCOS.

LncRNAs and Endometriosis

A notable down-regulation of lncRNA MALAT1 was observed in GCs of patients diagnosed with endometriosis. This down-regulation was found to be correlated with the number of antral follicles. Furthermore, the expression level of MALAT1 was significantly lower in cancer tissues from patients with endometriosis-associated infertility compared to the normal group.⁶⁴ In comparison to healthy controls, paraffin blocks of patients with endometriosis had up-regulated levels of lncRNA SNHG4 expression.⁶⁵ Most of the differentially expressed lncRNAs of patients were associated with the number of oocytes retrieved, the number of 2PN zygotes, and the number of embryos in the cleavage stage. These results suggest that the abnormal expression of lncRNAs is not only related to follicular development, but also to subsequent fertilization and embryonic development. A total of 37 mRNAs, 51 lncRNAs, and 101 circRNAs were detected to be differentially expressed in GCs of patients with ovarian endometriosis. A network comprising lncRNA-miRNA-mRNA interactions, primarily governing cell differentiation and the cell cycle, was constructed through the analysis of 10 differentially expressed lncRNAs and 22 mRNAs.⁶⁶ MUC20-OT1 was also discovered to be highly correlated with the expression of PRKAR2A, GPC6, SMC5, EIF3A, ITGAV, and PGRMC2. PGRMC2 was closely linked to the expressions of AC123912SMC5, EIF3A, PRKAR2A, ITGAV, and PGRMC2. LERFS was co-expressed with SMC5, PRKAR2A, ITGAV, and PGRMC2.⁶⁴ LncRNAs interact with miRNAs and mRNAs to regulate the expression of target genes to regulate oocyte development.

LncRNAs and Ovarian Insufficiency(POI)

In POI, the cortical tissue of ovaries contained 20 lncRNAs with variable expression, several of which were co-regulated.⁶⁷ Patients with limited ovarian reserve (DOR) had 244 up-regulated and 222 down-regulated lncRNAs in their GCs. According to bioinformatics analysis, “cell adhesion and apoptosis”, “steroid biosynthesis”, “immune system”, and other biological processes were considerably enriched in the differentially expressed lncRNAs genes.⁶⁸ Patients with DOR had lower expression of lnc-GULP1-2:1, but patients with PCOS had significantly higher reserve.⁶⁹ Duan et al discovered 78 lncRNAs differentially expressed in GCs of patients with premature ovarian failure (POF), among these, the significantly down-regulated lncRNA ZNF674-AS1 was positively correlated with serum basal estradiol and AMH levels, and negatively correlated with basal FSH levels.⁷⁰ H19 was moderately positively correlated with AMH in serum. H19 expression was 3.7-fold higher in GCs of patients with high ovarian response than those with low ovarian response.⁷¹ It can be seen that the dysfunction of lncRNAs in GC may be related to abnormal follicular development. Some lncRNAs found in patients’ GCs have been found to regulate or interact with miRNAs, and they mainly regulate cell proliferation, apoptosis, cell cycle, and ovarian function (Table 3).^{69,70,72-77}

LncRNAs and Ovarian Hyper-Stimulation Syndrome (OHSS)

High-throughput sequencing was used to analyze the differences in lncRNAs in GCs from high- and low-risk women with OHSS. A total of 23,815 lncRNAs were discovered, of which 482 were differentially expressed, 205 were up-regulated and 277 were down-regulated. Among the 7 lncRNAs with the most obvious differential expression, lnc-SEC16B.1-6, lnc-SNURF-13, lnc-LGR6-6, lncH2AFY2-2 were up-regulated, while lnc-BRD2-2, lnc-HSPA6-2, lnc-CLIC6-5 were down-regulated.⁷⁸ So, lncRNA may be involved in the occurrence of OHSS.

Conclusion

Several lncRNAs participate in multiple biological processes and their dysregulation frequently causes disease. According to recent studies, most regulatory lncRNAs interact with biological macromolecules such as DNA, RNA,

Table 3 LncRNAs in GCs of Patients with Ovarian Insufficiency

LncRNA	Up/Down Regulation	Regulate or Interact with miRNA or protein	Functions	Reference
GULPI-2:1	Down	COL3A1	Affect the proliferation of GCs	[69]
ZNF674-AS1	Down	PCNA and ALDOA	Inhibit glycolysis and proliferation of GCs.	[70]
DLEU1	Up	miR-146b-5p	Promote cell proliferation	[72]
BBOX1-AS1	Up	miR-146b	Affect the cell apoptosis	[73]
HCP5	Down	YBI	Regulate the transcription of MSH5 and DNA damage repair	[74]
PVT1	Down	Foxo3a	Promote the apoptosis of GCs	[75]
DANCR	Down	hNRPNC-p53 interaction	Inhibit cell growth and cause a G1 arrest in the cell cycle	[76]
H19	Down	Let-7	Regulate AMH expression	[77]

and proteins. LncRNAs primarily regulate gene expression through DNA methylation, histone modification, chromatin remodeling, including epigenetic modification, transcription, and post-transcription. Studies on lncRNAs and oocyte development have resulted in positive findings. LncRNAs have the potential to influence GCs, ovaries, and disease development through diverse pathways. Consequently, they may find utility in the diagnosis and treatment of various diseases.

Abbreviations

LncRNA, long non-coding RNAs; GC, granulosa cell; FSH, Follicle-Stimulating Hormone; MGC, mural granulosa cell; CC, Cumulus cell; PCOS, Polycystic Ovarian Syndrome; ceRNA, competing endogenous RNA; 2PN, two pronucleuses; POF, premature ovarian failure; AMH, anti-Mullerian hormone; PCNA, proliferating cell nuclear antigen; bPOI, biochemical ovarian insufficiency; DOR, diminished ovarian reserve; OHSS, Ovarian Hyper-stimulation Syndrome; ROMA, recurrent oocyte maturation arrest; GV, germinal vesicle; MI, metaphase; MII, metaphase II; LH, Luteinizing Hormone; Hcg, Human Chorionic Gonadotropin; PFA, primordial follicle activation.

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The authors report no conflicts of interest in this work.

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