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REVIEW

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

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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 quality[10] 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 lncRNAsare 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 TGFβ 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-AS1	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-AS1	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]
OC1	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 lncRNAd 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
GULP1-2:1	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	YB1	Regulate the transcription of MSH5 and DNA damage repair	[74]
PVT1	Down	Foxo3a	Promote the apoptosis of GCs	[75]
DANCR	Down	hNRNPC-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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Disclosure

The authors report no conflicts of interest in this work.

References

1. Akrami R, Jacobsen A, Hoell J, et al. Comprehensive analysis of Long non-coding RNAs in ovarian Cancer reveals global patterns and targeted DNA amplification. *PLoS One*. 2013;8:1–11. doi:10.1371/journal.pone.0080306
2. Xiong Y, Liu T, Wang S, et al. Cyclophosphamide promotes the proliferation inhibition of mouse ovarian granulosa cells and premature ovarian failure by activating the lncRNA-Meg3-p53-p66Shc pathway. *Gene*. 2017;596:1–8. doi:10.1016/j.gene.2016.10.011
3. Li J, Cao Y, Xu X, et al. Increased new lncRNAmRNA gene pair levels in human cumulus cells correlate with oocyte maturation and embryo development. *Reprod Sci*. 2015;22:1008–1014. doi:10.1177/1933719115570911
4. Bao B, Garyerick HA. Expression of steroidogenic enzyme and gonadotropin receptor genes in bovine follicles during ovarian follicular waves: a review. *Anim Sci*. 1998;76(7):1903–1921. doi:10.2527/1998.7671903x
5. Luo Y, Zhang R, Gao J, et al. The localization and expression of epidermal growth factor and epidermal growth factor receptor in bovine ovary during oestrous cycle. *Reprod Domest Anim*. 2020;55(7):822–832. doi:10.1111/rda.13690
6. Downs SM. The influence of glucose, cumulus cells, and metabolic coupling on ATP levels and meiotic control in the isolated mouse oocyte. *Dev Biol*. 1995;167(2):502–512. doi:10.1006/dbio.1995.1044

7. Li SH, Lin MH, Hwu YM, et al. Correlation of cumulus gene expression of GJA1, PRSS35, PTX3, and SERPINE2 with oocyte maturation, fertilization, and embryo development. *Reprod Biol Endocrinol*. 2015;13:93. doi:10.1186/s12958-015-0091-3
8. Assidi M, Montag M, Sirard MA. Use of both cumulus cells' transcriptomic markers and zona pellucida birefringence to select developmentally competent oocytes in human assisted reproductive technologies. *BMC Genomics*. 2015;16:S9. doi:10.1186/1471-2164-16-S1-S9
9. Kahraman S, Cetinkaya CP, Cetinkaya M, et al. Is there a correlation between follicle size and gene expression in cumulus cells and is gene expression an indicator of embryo development? *Reprod Biol Endocrinol*. 2018;16(1):69. doi:10.1186/s12958-018-0388-0
10. Wyse BA, Fuchs Weizman N, Kadish S, et al. Transcriptomics of cumulus cells - a window into oocyte maturation in humans. *J Ovarian Res*. 2020;13(1):93. doi:10.1186/s13048-020-00696-7
11. Fragouli E, Lalioti MD, Wells D. The transcriptome of follicular cells: biological insights and clinical implications for the treatment of infertility. *Hum Reprod Update*. 2014;20(1):1–11. doi:10.1093/humupd/dmt044
12. Okamura K. Diversity of animal small RNA pathways and their biological utility. *Wiley Interdiscip Rev RNA*. 2012;3:351–368. doi:10.1002/wrna.113
13. Wang KC, Chang HY. Molecular mechanisms of long noncoding RNAs. *Mol Cell*. 2011;43:904–914. doi:10.1016/j.molcel.2011.08.018
14. Mercer TR, Mattick JS. Structure and function of long noncoding RNAs in epigenetic regulation. *Nat Struct Mol Biol*. 2013;20:300–307. doi:10.1038/nsmb.2480
15. Sen R, Ghosal S, Das S, et al. Competing endogenous RNA: the key to posttranscriptional regulation. *ScientifcWorldJournal*. 2014;2014:896206.
16. Niu ZS, Wang WH, Dong XN, et al. Role of long noncoding RNA-mediated competing endogenous RNA regulatory network in hepatocellular carcinoma. *World J Gastroenterol*. 2020;26(29):4240–4260. doi:10.3748/wjg.v26.i29.4240
17. Statello L, Guo CJ, Chen LL, et al. Gene regulation by long non-coding RNAs and its biological functions. *Nat Rev Mol Cell Biol*. 2021;22(2):96–118. doi:10.1038/s41580-020-00315-9
18. Liang L, Ai L, Qian J, et al. Long noncoding RNA expression profiles in gut tissues constitute molecular signatures that reflect the types of microbes. *Sci Rep*. 2015;5:11763. doi:10.1038/srep11763
19. Martens-Uzunova ES, Böttcher R, Croce CM, et al. Long noncoding RNA in prostate, bladder, and kidney cancer. *Eur Urol*. 2014;65(6):1140–1151. doi:10.1016/j.eururo.2013.12.003
20. Arita T, Ichikawa D, Konishi H, et al. Circulating long non-coding RNAs in plasma of patients with gastric cancer. *Anticancer Res*. 2013;33(8):3185–3193.
21. Vance KW, Sansom SN, Lee S, et al. The long non-coding RNA Paupar regulates the expression of both local and distal genes. *EMBO J*. 2014;33(4):296–311. doi:10.1002/embj.201386225
22. Li J, Xuan Z, Liu C. Long non-coding RNAs and complex human diseases. *Int J Mol Sci*. 2013;14(9):18790–18808. doi:10.3390/ijms140918790
23. Clark MB, Mattick JS. Long noncoding RNAs in cell biology. *Semin Cell Dev Biol*. 2011;22(4):366–376. doi:10.1016/j.semcdb.2011.01.001
24. Wang P, Ren Z, Sun P. Overexpression of the long non-coding RNA MEG3 impairs in vitro glioma cell proliferation. *J Cell Biochem*. 2012;113(6):1868–1874. doi:10.1002/jcb.24055
25. Yan L, Yang M, Guo H, et al. Single-cell RNA-Seq profiling of human preimplantation embryos and embryonic stem cells. *Nat Struct Mol Biol*. 2013;20:1131–1139. doi:10.1038/nsmb.2660
26. Huang K, Maruyama T, Fan G. The naive state of human pluripotent stem cells: a synthesis of stem cell and preimplantation embryo transcriptome analyses. *Cell Stem Cell*. 2014;15:410–415. doi:10.1016/j.stem.2014.09.014
27. Bouckenheimer J, Assou S, Riquier S, et al. Long non-coding RNAs in human early embryonic development and their potential in ART. *Hum Reprod Update*. 2016;23:19–40. doi:10.1093/humupd/dmw035
28. Chow J, Heard E. X inactivation and the complexities of silencing a sex chromosome. *Curr Opin Cell Biol*. 2009;21:359–366. doi:10.1016/j.ceb.2009.04.012
29. Leeb M, Steffen PA, Wutz A. X chromosome inactivation sparked by non-coding RNAs. *RNA Biol*. 2009;6:94–99. doi:10.4161/rna.6.2.7716
30. Batista PJ, Chang HY. Long noncoding RNAs: cellular address codes in development and disease. *Cell*. 2013;152:1298–1307. doi:10.1016/j.cell.2013.02.012
31. Jiao J, Shi B, Wang TR, et al. Characterization of long non-coding RNA and messenger RNA profiles in follicular fluid from mature and immature ovarian follicles of healthy women and women with polycystic ovary syndrome. *Hum Reprod*. 2018;33:1735–1748. doi:10.1093/humrep/dey255
32. Zhang L, Zou J, Wang Z, Li L. A subpathway and target gene cluster-based approach uncovers lncRNAs associated with human primordial follicle activation. *Int J Mol Sci*. 2023;24(13):10525. doi:10.3390/ijms241310525
33. Wei L, Xia H, Liang Z, et al. Disrupted expression of long non-coding RNAs in the human oocyte: the possible epigenetic culprits leading to recurrent oocyte maturation arrest. *J Assist Reprod Genet*. 2022;39(10):2215–2225. doi:10.1007/s10815-022-02596-9
34. Ernst EH, Nielsen J, Ipsen MB, et al. Transcriptome analysis of long non-coding RNAs and genes encoding paraspeckle proteins during human ovarian follicle development. *Front Cell Dev Biol*. 2018;6:78. doi:10.3389/fcell.2018.00078
35. Yerushalmi GM, Salmon-Divon M, Yung Y, et al. Characterization of the human cumulus cell transcriptome during final follicular maturation and ovulation. *Mol Hum Reprod*. 2014;20(8):719–735. doi:10.1093/molehr/gau031
36. Yung Y, Ophir L, Yerushalmi GM, et al. HAS2-AS1 is a novel LH/hCG target gene regulating HAS2 expression and enhancing cumulus cells migration. *J Ovarian Res*. 2019;12:1–7. doi:10.1186/s13048-019-0495-3
37. Xu XF, Li J, Cao YX, et al. Differential expression of long noncoding RNAs in human cumulus cells related to embryo developmental potential: a microarray analysis. *Reprod Sci*. 2015;22(6):672–678. doi:10.1177/1933719114561562
38. Caponnetto A, Battaglia R, Ferrara C, et al. Down-regulation of long non-coding RNAs in reproductive aging and analysis of the lncRNA-miRNA-mRNA networks in human cumulus cells. *J Assist Reprod Genet*. 2022;39(4):919–931. doi:10.1007/s10815-022-02446-8
39. Bouckenheimer J, Fauque P, Lecellier CH, et al. Differential long non-coding RNA expression profiles in human oocytes and cumulus cells. *Sci Rep*. 2018;8(1):2202. doi:10.1038/s41598-018-20727-0
40. Chen Y, Zhang X, An Y, et al. LncRNA HCP5 promotes cell proliferation and inhibits apoptosis via miR-27a-3p/IGF-1 axis in human granulosa-like tumor cell line KGN. *Mol Cell Endocrinol*. 2020;503:110697. doi:10.1016/j.mce.2019.110697
41. Wang C, Yue S, Jiang Y, et al. LncRNA GAS5 is upregulated in polycystic ovary syndrome and regulates cell apoptosis and the expression of IL-6. *J Ovarian Res*. 2020;13(1):145. doi:10.1186/s13048-020-00748-y

42. Li Y, Liu YD, Chen SL, et al. Down-regulation of long non-coding RNA MALAT1 inhibits granulosa cell proliferation in endometriosis by up-regulating P21 via activation of the ERK/MAPK pathway. *Mol Hum Reprod*. 2019;25(1):17–29. doi:10.1093/molehr/gay045
43. Huang X, Hao C, Bao H, et al. Aberrant expression of long noncoding RNAs in cumulus cells isolated from PCOS patients. *J Assist Reprod Genet*. 2016;33:111–121. doi:10.1007/s10815-015-0630-z
44. Liu G, Liu S, Xing G, et al. lncRNA PVT1/MicroRNA-17-5p/PTEN Axis regulates secretion of E2 and P4, proliferation, and apoptosis of ovarian Granulosa cells in PCOS. *Mol Ther Nucleic Acids*. 2020;20:205–216. doi:10.1016/j.omtn.2020.02.007
45. Zhu HL, Chen YQ, Zhang ZF. Downregulation of lncRNA ZFAS1 and upregulation of microRNA-129 repress endocrine disturbance, increase proliferation and inhibit apoptosis of ovarian granulosa cells in polycystic ovarian syndrome by downregulating HMGB1. *Genomics*. 2020;112:3597–3608. doi:10.1016/j.ygeno.2020.04.011
46. Sang X, Zhang YZ. Long Non-coding RNA NEAT1 drives the development of polycystic ovary syndrome via sponging multiple MicroRNA. *Cell Biol Int*. 2020;2020:1. doi:10.1002/cbin.11349
47. Guo H, Li T, Sun X. LncRNA HOTAIRM1, miR-433-5p and PIK3CD function as a ceRNA network to exacerbate the development of PCOS. *J Ovarian Res*. 2021;14(1):19. doi:10.1186/s13048-020-00742-4
48. Li G, Wang Y, Wang J, et al. Long non-coding RNA placenta-specific protein 2 regulates micorRNA-19a/tumor necrosis factor α to participate in polycystic ovary syndrome. *Bioengineered*. 2022;13(1):856–862. doi:10.1080/21655979.2021.2013722
49. Guo Y, Peng X, Cheng R, et al. Long non-coding RNA-X-inactive specific transcript inhibits cell viability, and induces apoptosis through the microRNA-30c-5p/Bcl2-like protein 11 signaling axis in human granulosa-like tumor cells. *Bioengineered*. 2022;13(6):14107–14117. doi:10.1080/21655979.2022.2080366
50. Chen Z, Liu L, Xi X, et al. Aberrant H19 expression disrupts ovarian Cyp17 and testosterone production and is associated with polycystic ovary syndrome in women. *Reprod Sci*. 2022;29(4):1357–1367. doi:10.1007/s43032-021-00700-5
51. Sun X, Yan X, Liu K, et al. LncRNA H19 acts as a ceRNA to regulate the expression of CTGF by targeting miR-19b in polycystic ovary syndrome. *Braz J Med Biol Res*. 2020;53(11):e9266. doi:10.1590/1414-431x20209266
52. Huang Y, Zhang Y, Zhou Y, et al. CDKN2B-AS1 is overexpressed in polycystic ovary syndrome and sponges miR-181a to promote granulosa cell proliferation. *Anticancer Drugs*. 2023;34(2):207–213. doi:10.1097/CAD.0000000000001405
53. Jin L, Yang Q, Zhou C, et al. Profiles for long noncoding RNAs in ovarian granulosa cells from women with PCOS with or without hyperandrogenism. *Reprod BioMed Online*. 2018;37:613–623. doi:10.1016/j.rbmo.2018.08.005
54. Liu Y, Li Y, Feng S, et al. Long noncoding RNAs: potential regulators involved in the pathogenesis of polycystic ovary syndrome. *Endocrinology*. 2017;158:3890–3899. doi:10.1210/en.2017-00605
55. Yang R, Chen J, Wang L, et al. LncRNA BANCR participates in polycystic ovary syndrome by promoting cell apoptosis. *Mol Med Rep*. 2019;19:1581–1586. doi:10.3892/mmr.2018.9793
56. Che Q, Liu M, Zhang D, et al. Long noncoding RNA HUPCOS promotes follicular fluid androgen excess in PCOS patients via aromatase inhibition. *J Clin Endocrinol Metab*. 2020;105:1–12. doi:10.1210/clinem/dgaa060
57. Li Y, Zhang J, Liu YD, et al. Long non-coding RNA TUG1 and its molecular mechanisms in polycystic ovary syndrome. *RNA Biol*. 2020;17(12):1798–1810. doi:10.1080/15476286.2020.1783850
58. Xiang Y, Yu G, Song Y, et al. The Upregulation of HAS2-AS1 Relates to the Granulosa Cell Dysfunction by Repressing TGF-βSignaling and Upregulating HAS2. *Mol Cell Biol*. 2022;42(9):e0010722. doi:10.1128/mcb.00107-22
59. Geng X, Zhao J, Huang J, et al. lnc-MAP3K13-7:1 Inhibits Ovarian GC Proliferation in PCOS via DNMT1 downregulation-mediated CDKN1A promoter hypomethylation. *Mol Ther*. 2021;29(3):1279–1293. doi:10.1016/j.ymthe.2020.11.018
60. Wu G, Yang Z, Chen Y, et al. Downregulation of Lnc-OC1 attenuates the pathogenesis of polycystic ovary syndrome. *Mol Cell Endocrinol*. 2020;506:110760. doi:10.1016/j.mce.2020.110760
61. Zhang D, Yuan TH, Tan L, et al. MALAT1 is involved in the pathophysiological process of PCOS by modulating TGFβ signaling in granulosa cells. *Mol Cell Endocrinol*. 2020;499:110589. doi:10.1016/j.mce.2019.110589
62. Li Y, Xiang Y, Song Y, Zhang D, Tan L. MALAT1 downregulation is associated with polycystic ovary syndrome via binding with MDM2 and repressing P53 degradation. *Mol Cell Endocrinol*. 2022;543:111528. doi:10.1016/j.mce.2021.111528
63. Tu M, Wu Y, Wang F, et al. Effect of lncRNA MALAT1 on the granulosa cell proliferation and pregnancy outcome in patients with PCOS. *Front Endocrinol*. 2022;13:825431. doi:10.3389/fendo.2022.825431
64. Shi L, Wei X, Wu B, et al. Molecular signatures correlated with poor IVF outcomes: insights from the mRNA and lncRNA expression of endometriotic granulosa cells. *Front Endocrinol*. 2022;13:825934. doi:10.3389/fendo.2022.825934
65. Szaflik T, Romanowicz H, Szyłło K, et al. Long non-coding RNA SNHG4 expression in women with endometriosis: a pilot study. *Genes*. 2023;14(1):152. doi:10.3390/genes14010152
66. Guo J, Zeng H, Li T, et al. mRNA, lncRNA and Circular RNA expression profiles in granulosa cells of infertile women with ovarian endometriosis. *Reprod Sci*. 2022;29(10):2937–2946. doi:10.1007/s43032-022-00966-3
67. Yao G, He J, Kong Y, et al. Transcriptional profiling of long noncoding RNAs and their target transcripts in ovarian cortical tissues from women with normal menstrual cycles and primary ovarian insufficiency. *Mol Reprod Dev*. 2019;86(7):847–861. doi:10.1002/mrd.23158
68. Dong L, Xin X, Chang HM, et al. Expression of long noncoding RNAs in the ovarian granulosa cells of women with diminished ovarian reserve using high-throughput sequencing. *J Ovarian Res*. 2022;15(1):119. doi:10.1186/s13048-022-01053-6
69. Yao G, Kong Y, Yang G, et al. Lnc-GULP1-2:1 affects granulosa cell proliferation by regulating COL3A1 expression and localization. *J Ovarian Res*. 2021;14(1):16. doi:10.1186/s13048-021-00769-1
70. Li D, Wang X, Li G, et al. LncRNA ZNF674-AS1 regulates granulosa cell glycolysis and proliferation by interacting with ALDOA. *Cell Death Discov*. 2021;7(1):107. doi:10.1038/s41420-021-00493-1
71. Xia X, Burn MS, Chen Y, et al. The relationship between H19 and parameters of ovarian reserve. *Reprod Biol Endocrinol*. 2020;18(1):46. doi:10.1186/s12958-020-00578-z
72. Zheng C, Liu S, Qin Z, et al. LncRNA DLEU1 is overexpressed in premature ovarian failure and sponges miR-146b-5p to increase granulosa cell apoptosis. *J Ovarian Res*. 2021;14(1):151. doi:10.1186/s13048-021-00905-x
73. Yu Y, Zhang Q, Sun K, et al. Long non-coding RNA BBOX1 antisense RNA 1 increases the apoptosis of granulosa cells in premature ovarian failure by sponging miR-146b. *Bioengineered*. 2022;13(3):6092–6099. doi:10.1080/21655979.2022.2031675

74. Wang X, Zhang X, Dang Y, et al. Long noncoding RNA HCP5 participates in premature ovarian insufficiency by transcriptionally regulating MSH5 and DNA damage repair via YB1. *Nucleic Acids Res*. 2020;48(8):4480–4491. doi:10.1093/nar/gkaa127
75. Wang F, Chen X, Sun B, et al. Hypermethylation-mediated downregulation of lncRNA PVT1 promotes granulosa cell apoptosis in premature ovarian insufficiency via interacting with Foxo3a. *J Cell Physiol*. 2021;236(7):5162–5175. doi:10.1002/jcp.30222
76. Sun D, Wang Y, Sun N, et al. LncRNA DANCR counteracts premature ovarian insufficiency by regulating the senescence process of granulosa cells through stabilizing the interaction between p53 and hNRNPC. *J Ovarian Res*. 2023;16(1):41. doi:10.1186/s13048-023-01115-3
77. Qin C, Xia X, Fan Y, et al. A novel, noncoding-RNA-mediated, post-transcriptional mechanism of anti-Mullerian hormone regulation by the H19/let-7 axis. *Biol Reprod*. 2019;100(1):101–111. doi:10.1093/biolre/ioy172
78. Lin H, Li Y, Xing W, et al. Genome-wide screening differential long non-coding RNAs expression profiles discloses its roles involved in OHSS development. *J Assist Reprod Genet*. 2018;2:1473–1482. doi:10.1007/s10815-018-1199-0