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Chapter

Roles of ncRNAs in Ovarian Dysfunction of Polycystic Ovary Syndrome

Junyong Han, Zhen Yu, Gang Chen and Fan Wang

Abstract

Polycystic ovary syndrome (PCOS) is a common endocrine disease in women of childbearing age. Many heterogeneous clinical manifestations of PCOS, including hyperandrogenism, obesity, insulin resistance, hirsutism, acne, chronic anovulation and infertility, seriously affected the quality of life of women worldwide and made it difficult to clearly demonstrate the specific pathophysiology. In recent years, large-scale studies have shown that non-coding RNAs (ncRNAs) play an important role in the regulation of ovarian functions, which did not have the ability to encode proteins and could regulate hormone synthesis and germ cell development, differentiation, and apoptosis by silencing transposable elements and regulating coding genes. A number of researches by whole transcriptome sequencing of polycystic ovaries (PCO) from PCOS patients or PCOS model animals found that the abnormal expressions of many ncRNAs were involved in the regulation of ovarian dysfunctions of PCOS, including the development of oocytes, the microenvironment of follicular fluid, and the proliferation, differentiation, and apoptosis of granulosa cells. The present review focused on the roles of ncRNAs in the PCO of PCOS, in order to provide a theoretical basis for further understanding of the molecular mechanisms of PCO formation in PCOS.

Keywords: ncRNAs, granule cell, oocyte, follicle fluid, polycystic ovary syndrome

1. Introduction

Polycystic ovary syndrome (PCOS) is an endocrine and reproductive disease in women that often occurs during the childbearing years [1]. PCOS is closely related to metabolic syndrome, and has become an increasingly serious public health problem worldwide, these patients have an increased risk of endometrial cancer, type 2 diabetes, and cardiovascular disease. The clinical characteristics of PCOS women show heterogeneity, include excessive androgen, infertility, obesity, anovulation, irregular menstruation, polycystic ovaries (PCO), hairy and recurrent miscarriage, insulin resistance and abnormal blood lipids [2].

Anovulatory infertility of PCOS patients accounts for more than 75%, and the spontaneous abortion rate of them in early pregnancy is 30–50% [3, 4]. Ovulation failure (such as ovulation or anovulation) is the main clinical features of PCOS. There are a large number of small follicles in the bilateral ovaries of PCOS patients, which can not grow into dominant follicle, suggesting the occurrence of follicular dysplasia [5]. The processes of ovarian follicular development and atresia

are a complex and delicate. However, ovulatory dysfunction in PCOS women is related to various factors such as abnormalities in proliferation and apoptosis of granule cells (GCs) and in follicular development and atresia. As is well-known that GCs are involved in the normal development and maturation of follicles. Some studies have found that the proliferation rate of GCs in PCOS patients is significantly higher, and the apoptotic rate is significantly lower [6, 7] suggesting that abnormalities in the proliferation and apoptosis of GCs may be a pathogenic mechanism of ovarian dysfunction of PCOS.

Due to the complexity of the etiology of PCOS, its specific pathophysiology has not yet been fully elucidated. More and more researches are currently being conducted to analyze the gene expression profiling of PCOS at the mRNA and protein levels, in order to explore its molecular mechanisms. PCOS is caused by the imbalance of multiple gene pathways [8]. The candidate genes are involved in sex hormone synthesis, insulin synthesis, chronic inflammatory factors, lipid metabolism, cell proliferation and apoptosis [8]. With the advancement of RNA sequencing technologies, many researchers have discovered that non-coding RNA (ncRNA, which refers to a class of RNA without open reading frame and can not translate into proteins) is involved in the regulation of numerous cell signaling pathways and biological processes for life activities, such as cell development, differentiation, apoptosis and hormone synthesis, and the occurrence and development of diseases [9].

Most of the human genome is transcribed into various ncRNAs, MicroRNA (miRNA) and long-chain non-coding RNAs (lncRNA) are hotspots for studying novel biomarkers and therapeutic targets in related diseases in recent years, such as cancer [10], diabetes [11] and PCOS [9]. Recent studies have shown that both miRNA and lncRNA play an important role in the pathogenesis of PCOS [9, 12]. miRNA and lncRNA can directly or indirectly affect the normal physiological functions of the ovaries, include the growth and development of follicles and oocytes [9, 12]. Moreover, ovarian dysfunction in PCOS seriously affects the reproductive capacity in reproductive women, but its specific molecular mechanism is not yet known. This chapter focuses on the roles of several ncRNAs in PCOS ovaries in recent years, which will help to further elucidate its pathogenesis and to discover new therapeutic targets.

2. ncRNA

ncRNAs as enzyme, regulatory signal, molecular sink, ligand, organizer of cellular structures, potential hormone and scaffold of molecular interactions, can play an important role in cell physiology and abnormal biological processes, such as nuclear transport, transcriptional regulation of genes, protein degradation, genomic imprinting and X chromosome silencing [13].

2.1 miRNAs

miRNAs are 21–23 nucleotides in length and widely found in eukaryotes, which can predict post-transcriptional regulation of at least half of the human transcriptome [14–16]. Mature miRNA is formed by removing and processing a longer primary transcript through a series of nucleases [17–19]. The main function of miRNAs is silencing or degrading the expressions of target genes at the post-transcriptional level by forming an RNA-induced silencing complex [20]. Abnormal expressions of miRNAs are associated with insulin resistance [21, 22], diabetes [11, 22, 23], inflammation [20, 23] and various cancer formations [10]. The expression profiles of some

miRNAs in ovarian various cells and follicular fluids of PCOS patients exist significant differences, which had been involved in the occurrence and development of PCOS by affecting the post-transcriptional regulation of the target genesw [9, 12, 24].

2.2 lncRNAs

lncRNAs are a class of non-coding RNAs transcripts longer than 200 nucleotides in length, which produced by 4–9% of the sequence in mammalian genome [25, 26]. lncRNAs play critical roles in various human biological processes, such as chromatin modification, cell differentiation, proliferation and apoptosis, translational and post-translational regulation. Moreover, the abnormally expressed lncRNAs are involved in the occurrence and development of a variety of human diseases [27]. In recent years, more and more evidence has shown that lncRNAs are abnormally expressed in ovarian cumulus cells and/or GCs of PCOS patients [9, 28, 29]. These lncRNAs may be involved in ovarian steroid production, steroid receptor activity and IR, and future affect ovarian cell development, proliferation and apoptosis, which in turn leads to the occurrence of ovarian dysfunction of PCOS [28, 29].

3. PCO

PCO is one of the diagnostic indicators and symptoms for PCOS, which imaged the ovaries with ultrasound showing ≥12 follicles (each follicle is 2–9 mm in diameter) on one or both sides, and/or an ovarian volume ≥10 ml [5]. During the development and maturation of ovarian follicles, the oocyte interconnected and interdependent with surrounding GCs. The development of an oocyte requires GCs to provide nutrients, corresponding hormones and growth regulators [30, 31]. Abnormal interactions between GCs and oocytes are a possible cause of ovarian follicular dysplasia in PCOS [32]. Some vitro fertilization studies found that PCOS patients have a lower rate of implantation than normal women [33–35]. Microarray analysis indicated that abnormal endocrine and metabolism affect gene expression of oocytes in PCOS ovaries [36].

Moreover, ovarian follicular fluid is a fluid that fills the follicular cavity and surrounds cumulus cells. Follicular fluid is rich in substances such as hormones, growth factors, anti-apoptotic antibodies, various proteins, peptides, amino acids and nucleotides. Studies have confirmed that these substances are closely related to female reproductive system diseases, embryo quality and in vitro fertilization outcomes [37]. Therefore, the homeostasis of the microenvironment of follicular fluid directly affects follicular development and oocytes quality.

It is well known that insulin resistance and hyperinsulinemia play an important role in the pathophysiology of PCOS. Studies have found that most of PCOS patients with varying degrees of IR and compensatory hyperinsulinemia, including ovarian IR [38]. Ovarian GCs in PCOS patients are impaired by insulin-dependent glucose metabolism [38, 39]. Damaged glucose metabolism reduces the energy supply to GCs and oocytes, and thus hinders the proliferation of GCs and the development of oocytes [38, 39]. Therefore, GCs dysfunction is contributed to abnormal ovarian function in PCOS, including anovulation. Moreover, excessive apoptosis of cumulus GCs directly causes follicular dysplasia in PCOS, which are correlated with changes in ncRNAs expression profiles in follicular fluid. The abnormal expressions of ncRNAs from the ovaries of PCOS may contribute to its occurrence and development [9, 12, 40].

4. Effects of ncRNAs on ovarian dysfunction of PCOS

With the development of RNA sequencing technologies, many researchers have carried out miRNA or lncRNA sequencing studies on the ovaries of PCOS, in order to detect the molecular mechanisms of ovarian dysfunction. Studies have shown that compared with control rats, there are 129 miRNAs (49 miRNAs are up-regulated, 80 miRNAs are down-regulated) and 158 lncRNAs (114 lncRNAs are up-regulated, 44 lncRNAs are down-regulated) by deep-sequencing of ovaries tissue from letrozole-induced PCOS rats [41, 42]. Gene ontology (GO) and Kyoto encyclopedia of genes and genomes (KEG) Genes pathway analyzed and predicted that the differentially expressed ncRNAs in PCOS ovaries may be associated with abnormal ovarian GCs proliferation, apoptosis and steroidogenesis and ovarian insulin resistance [41, 42].

4.1 Roles of ncRNAs in the proliferation and apoptosis of GCs

4.1.1 miR-141-3p

In the ovaries of PCOS rat model, the expression of miR-141-3p is significantly decreased, which can target to death-associated protein kinase 1 (DAPK1) and mitogen-activated protein kinase 1 (MAPK1) signaling pathway to inhibit apoptosis of GCs, or regulate mitochondria-mediated apoptosis through phosphatidylinositol 3 kinase/protein kinase B (PI3K/Akt) and extracellular protein kinase (ERK) signaling pathways, and thus suppressing cell growth, promoting cell apoptosis, and further leading to the development of PCOS [41].

4.1.2 miR-483-5p

miR-483-5p is the most abundant known miRNA in human ovarian follicular fluid [43]. miR-483-5p is highly expressed in cumulus granulosa cells and follicular fluid of PCOS patients [44]. In PCOS cumulus cells, high concentrations of miR-483-5p hinders the expressions of Notch3 and MAPK3 protein by binding to the 3′UTR terminus of their mRNA, thereby blocking the Notch signaling pathway and the MAPK signaling pathway (the two pathways play an important role in cell proliferation, differentiation and apoptosis), which inhibits the proliferation and differentiation of cumulus GCs and promoted the apoptosis of GCs [44].

4.1.3 LncRNA CD36-005

lncRNA CD36-005 is a transcript encoding the fatty acid transporter CD36 gene, which may be involved in cell growth, development, transport, and metabolism by bioinformatics analysis [42, 45]. lncRNA CD36-005 is expressed in rat ovaries, and its expression level is related to the estrous cycle, which indicates that it plays a role in animal reproductive activities [45]. Moreover, the study found that lncRNA CD36-005 and CD36 were highly expressed in the ovaries of PCOS rats by high-throughput sequencing and qRT-PCR verification. lncRNA CD36-005 significantly inhibits the proliferation of GCs by reducing the viability and the S phase of the cell cycle, which may be involved in the pathogenesis of PCOS [42].

4.2 Roles of ncRNAs in ovarian steroidogenesis

4.2.1 miR-320

miR-320 is closely related to PCOS, especially in the process of follicular development [46, 47]. miR-320 can regulate the translation of its target genes by

post-transcriptional regulation, thereby improving the levels of steroid hormones. miR-320 was down-regulated in cumulus GCs from PCOS ovaries [48], and its expression in follicular fluid was controversial [49]. miR-320 deficiency not only impairs the expression of the steroid synthase CYP11A1 and CYP19A1, but also enhances the steroidogenesis in CGs by directly regulating the RUNX2/CYP11AI cascade in the 3′UTR of Runx2, indicating that the cascade are a possible mechanism for the lack of estrogen synthesis in GCs of PCOS patients. In addition, miR-320 can target transcriptional factors E2F1 and steroidogenic factor-1 (SF-1) to inhibit the proliferation of GCs, and promote the synthesis of testosterone and progesterone [47].

4.2.2 LncRNA HCG26

lncRNA HCG26 is mainly distributed in the nucleus of ovarian GCs, which is highly expressed in PCOS patients [29]. HCG26 knockout can promote aromatase gene expression and estradiol synthesis, but can not affect the levels of androstenedione and follicle stimulating hormone, suggesting lncRNA HCG26 is involved in abnormal ovarian steroidogenic synthesis [50]. Moreover, the study also found that lncRNA HCG26 deficiency inhibits the proliferation of GCs and its expression correlated with the number of PCOS ovarian follicles, suggesting that lncRNA HCG26 may affect the proliferation of GCs and contributes to the formation of polycystic ovary morphology [29].

4.3 Roles of ncRNAs in ovarian insulin resistance

4.3.1 miR-92

Down-regulation of miR-92a/b expression in PCOS patients is associated with insulin resistance, hyperinsulinemia and hyperandrogenism [24], which can increase the expression of its target gene IRS-2, which activates the insulin signaling pathway in the ovaries of PCOS patients, thereby leading to be involved in the process of insulin resistance and hyperinsulinemia [24, 29].

4.3.2 miR-145

miR-145 overexpression in GCs of PCOS patients inhibits the target gene IRS1 and MAPK/ERK signaling pathways, and promotes the activity of PI3K/Akt signaling pathway through negative feedback, thereby improving IR in PCOS patients [7, 24, 50].

5. Conclusions

PCOS is a chronic disease that affects the patients throughout their lives. However, there is currently no gene that is recognized as the determinant of the pathogenesis of PCOS. Although the differential expression of ncRNAs in the ovaries from PCOS are involving in ovarian steroidogenesis, insulin resistance, cell proliferation and apoptosis and affect follicular development by regulating the expression of corresponding target genes at the post-transcriptional level, there are still many ncRNAs and the specific mechanism of their action in ovarian function of PCOS have not been discovered. Moreover, the roles and mechanisms of lncRNAs in PCOS have just been carried out, and the focus is on the study of lncRNA in peripheral blood of the patients or animal models, that in ovarian tissue is limited. The interactions between ncRNAs in PCOS have not been reported, such as miRNA-miRNA, lncRNA-lncRNA, and miRNA-lncRNA. Solving these problems will be contribution to further understand the etiology and pathogenesis of PCOS.

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Conflict of interest

The authors declare no conflict of interest.

A. Appendices

PCOS	polycystic ovary syndrome
ncRNAs	non-coding RNA
PCO	polycystic ovary
GCs	granule cells
lncRNA	long-chain non-coding RNAs
GO	gene ontology
KEGG	Kyoto encyclopedia of genes and genomes
DAPK1	death-associated protein kinase 1
MAP K1	mitogen-activated protein kinase 1
PI3K/Akt	phosphatidylinositol 3 kinase/protein kinase B
ERK	extracellular protein kinase
SF-1	steroidogenic factor-1

Author details

Junyong Han[1], Zhen Yu[1], Gang Chen[1] and Fan Wang[1,2,3]*

1 Fujian Provincial Key Laboratory of Medical Analysis, Fujian Academy of Medical Sciences, Fuzhou, China

2 State Key Laboratory for Evaluation of Exercise Physiological Functions from General Administration of Sport of China, School of Physical Education and Sport Sciences, Fujian Normal University, Fuzhou, China

3 Laboratory of Sport Physiology and Biomedicine, School of Physical Education and Sport Sciences, Fujian Normal University, Fuzhou, China

*Address all correspondence to: 517239819@qq.com

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