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MINI REVIEW

Role of circular RNA/miRNA axes in the pathophysiology of polycystic ovary syndrome

Mohsen Ahmadi[1] · Mohadeseh Fathi[1] · Ali Malmir[2] · Soudeh Ghafouri-Fard[3]

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Abstract
Polycystic ovary syndrome (PCOS) is a disorder resulted from interactions between genetic and environmental factors. Based on the importance of epigenetic factors in the pathoetiology of PCOS, the current review focused on identification of circular RNAs (circRNAs) that are involved in PCOS through acting as molecular sponges for microRNAs (miRNAs). The literature search led to identification of circ_0043533/miR-1179, circ_0030018/miR-136, circ_FURIN/miR-423-5p, circ-FURIN/miR-195-5p, circ_0043532/miR-182, circ_RANBP9/miR-136-5p, circRHBG/miR-515-5p, circMTO1/miR-320b, circASPH/miR-375, circPSMC3/miR-296-3p, circLDLR/miR-1294, circPUM1/miR-760, and hsa_circ_0118530/miR-136 as molecular axes contributing to the pathogenesis of PCOS. To set the stage for future research on the role of the ceRNA network in PCOS, *in-silico* analyses were performed using miRWalk, miRNet, and miRDIP databases. miRWalk identified 80 genes regulated by 5 miRNAs, miRNet revealed 6449 circRNAs potentially controlling 11 miRNAs, and miRDIP identified 11 miRNAs associated with 35 human pathways. These targets can be used in the treatment options, design of personalized medicine and prediction of prognosis of PCOS.

Keywords circRNA · miRNA · ceRNA · PCOS

Introduction

Polycystic ovary syndrome (PCOS) is a common disorder affecting females during the reproductive age. This condition can result in hormonal imbalance, irregular menstruations, excess androgen level and cysts in the ovaries. It is frequently associated with lack of ovulation and subsequent infertility [1]. PCOS is known as a complex metabolic condition that is expressed in genetically vulnerable females after a variety of negative exposures to the dietetic and environmental influences associated with modern lifestyle [2]. A novel evolutionary model has been suggested for description of the pathoetiology of PCOS. This model integrates a wide array of evidence came from the evolutionary theory, genetic investigations, epigenetic programming during fetal period, trans-generational inheritance, and metabolic features [2].

PCOS results from interactions between environmental and genetic factors. However, genetic factors explain less than 10% of PCOS susceptibility [3–5]. A large-scale genome wide study has provided evidence for participation of several genetic *loci* in the pathogenesis of PCOS and comparable genetic characteristics for all PCOS diagnostic standards [6]. Several susceptibility *loci* have been found for PCOS suggesting that diverse phenotypes and sub-phenotypes result from uncommon genetic variants [7]. Meanwhile, the importance of epigenetic factor should not be ignored in this condition. The observed alterations in the methylation profile of DNA and miRNAs in different biological sources from PCOS subjects indicate that these patients have a different epigenetic regulation. This abnormal epigenetic regulation can be induced by an unfavorable intrauterine milieu or by postnatal environmental factors, including nutritional conditions or obesity [8]. The current review focuses on the role of circular RNAs (circRNAs)

✉ Soudeh Ghafouri-Fard
s.ghafourifard@sbmu.ac.ir

[1] Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2] Department of Molecular Genetics, Faculty of Biological Sciences, Tarbiat Modares University, Tehran, Iran

[3] Department of Medical Genetics, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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as molecular sponges for microRNAs (miRNAs) in the pathoetiology PCOS.

CircRNAs as epigenetic regulators

CircRNAs are a class of non-coding RNAs that are detected in varied range of cells in diverse tissues across species. These non-polyadenylated, single-stranded, covalently enclosed transcripts are resistant to exonuclease digestion [9]. They have some important features, including diversity, stable structure, conservation during evolution, and specific expression signature. These features give circRNAs several vital biological functions. Therefore, circRNAs are regarded as regulator of physiological processes as well as pathological conditions. In addition to the regulation of transcription and splicing, they act as miRNA sponges to affect expression of miRNA targets [10].

The impact of circRNAs in the pathogenesis of PCOS-associated pathologies

CircRNAs contribute to the pathogenesis of several metabolic disorders, including obesity [11], insulin resistance [12] and diabetes [13]. Most importantly, the role of circRNAs in diverse pathologies related with infertility has been recently acknowledged [14, 15]. Certain circRNA signature has been associated with success rate of assisted reproductive technology. To be more specific, circRNA_103829, circRNA_103827 and circRNA_104816 have been up-regulated, whereas circRNA_101889 has been down-regulated in ovarian granulosa cells (OGCs) obtained from females with advanced age [16]. From a mechansitical viewpoint, circRNA_103827 and circRNA_104816 have a role in the regulation of ANKRD20A9P, KCNQ1OT1 and XIST, possibly through regulation of has-miR-4500, has-miR-4458, has-miR-3187-5p and has-miR-98-5p [16]. Since circRNA_103827 and circRNA_104816 have shown an age-related up-regulation in OGCs, they have been suggested as possible indicators of unfavorable follicular microenvironment and predictors of IVF prognosis [16]. Thus, several clues point to the involvement of circRNAs in the pathophysiology of PCOS-related conditions.

CircRNA/miRNA axes in PCOS

A number of studies have validated circRNA/miRNA axes in PCOS using appropriate experiments (Table 1). For instance, Chen et al. have demonstrated up-regulation of circ_0043533 in OGCs and insulin-treated OGCs. They have also examined the interaction between this circRNA and miR-1179 using bioinformatics tools, as well as dual-luciferase and RNA immunoprecipitation assays. Circ_0043533 silencing has significantly decreased viability and proliferation and enhanced apoptosis of insulin-treated OGCs. In the meantime, circ_0043533 silencing could decrease expression levels of Bcl-2, CDK2, and Cyclin D1, and enhance Bax expression. Mechanistically, circ_0043533 acts as a sponge to engage miR-1179. Remarkably, miR-1179 suppression has weakened the effects of circ_0043533 silencing on proliferation and apoptosis of insulin-treated OGCs. Cumulatively, circ_0043533/miR-1179 axis has been found to contribute to the pathogenesis of PCOS [17]. Circ_0030018/miR-136 axis is another molecular axis participating in the progression of PCOS as revealed by Xu et al. [18]. Interactions between these two transcripts have been verified through luciferase reporter and RNA pull-down experiments. Expression of circ_0030018 has been shown to be elevated in PCOS patients and granulosa tumor cells (KGN cells). Circ_0030018 silencing has suppressed proliferation, migration, and invasion of these cells, and promoted their apoptosis. This circRNA could adsorb miR-136, a miRNA that targets MIEN1 [18]. miR-136-5p has also been found to be sponged by another circRNA, namely circ_RANBP9 in the context of PCOS. Notably, circ_RANBP9 silencing has repressed proliferation and increased apoptosis of KGN and COV434 cells, while miR-136-5p silencing has reversed these processes. In addition, XIAP, a target of miR-136-5p could abolish the effects of miR-136-5p on proliferation and apoptosis [19]. hsa_circ_0118530 is another circRNA that sponges miR-136. Expression of this circRNA has been highly elevated in PCOS patients and OGCs compared to controls. hsa_circ_0118530 silencing has led to up-regulation of E-cadherin and depression of N-cadherin. Notably, hsa_circ_0118530 silencing could inhibit ROS accumulation and MDA levels whereas inducing SOD activity. Moreover, hsa_circ_0118530 down-regulation could suppress release of inflammatory cytokines [20].

Figure 1A shows the mechanistic process underlying contribution of miR-136 in PCOS.

Circ_FURIN is another circRNA that affects PCOS pathogenesis through sponging at least two miRNAs. Expression of circ_FURIN has been found to be up-regulated in the ovarian cortex tissue of PCOS cases and TTR-treated KGN cells, parallel with up-regulation of MTM1 and down-regulation of miR-423-5p. Circ_FURIN silencing has alleviated TTR-induced proliferation suppression and apoptosis enhancement. Furthermore, silencing of miR-423-5p, a target of circ_FURIN, has decreased circ_FURIN silencing-mediated effect under TTR exposure. Thus, circ_FURIN/ miR-423-5p/MTM1 axis has a prominent role in the pathoetiology of PCOS [20]. This circRNA can also

Table 1 CircRNA/miRNA axes in PCOS.

Circular RNA	miRNA	Method	Pathway	Protein	Ref
circ_0043533	miR-1179	qRT-PCR	Cell viability Proliferation Apoptosis	Bcl-2 CDK2 Cyclin D1 Bax	[17]
circ_0030018	miR-136	qPCR	Proliferation Migration Invasion Apoptosis	MIEN1	[18]
circ_FURIN	miR-423-5p	qRT-PCR	TTR-induced proliferation TTR-induced apoptosis	MTM1	[29]
circ-FURIN	miR-195-5p	qRT-PCR	Proliferation Apoptosis	BCL2	[21]
circ_0043532	miR-182	qRT-PCR	Proliferation Cell cycle Apoptosis	SGK3	[22]
circ_RANBP9	miR-136-5p	qRT-PCR	Proliferation Apoptosis	XIAP	[19]
circRHBG	miR-515-5p	qRT-PCR	Proliferation Ferroptosis	SLC7A11	[23]
circMTO1	miR-320b	qRT-PCR	Proliferation Apoptosis	MCL1	[24]
circASPH	miR-375	qRT-PCR	Proliferation Apoptosis	MAP2K6	[25]
circPSMC3	miR-296-3p	qRT-PCR	Proliferation Apoptosis	PTEN	[27]
circLDLR (hsa_circ_0006877)	miR-1294	RNA sequencing	Estrogen (E2) secretion	CYP19A1	[28]
circPUM1	miR-760	qRT-PCR	Cell viability Apoptosis	-	[26]
hsa_circ_0118530	miR-136	qRT-PCR	Cell viability Cell migration Apoptosis	-	[20]

regulate apoptotic signaling pathways, since its up-regulation in PCOS cases has been associated with up-regulation of BCL2 via adsorbing miR-195-5p [21]. Figure 1B shows the mechanism of involvement of circ_FURIN in the pathogenesis of PCOS.

Circ_0043532 is another up-regulated circRNA in PCOS OGCs and KGN cells. Circ_0043532 knock-down has inhibited proliferation and cell cycle transition and stimulated cell apoptosis in the mentioned cells. Mechanistic analyses have shown that circ_0043532 sponges miR-182, a miRNA that targets SGK3. Therefore, circ_0043532/miR-182/SGK3 axis is another molecular axis contributing to the pathogenesis of PCOS [22].

Another study has used high-throughput chips to assess expression of circRNAs in PCOS cases. This study has shown up-regulation of circRHBG in OGCs of these patients. Knockdown of this circRNA has inhibited proliferation of KGN and SVOG cells. Further studies have shown that circRHBG contests with SLC7A11 to bind to miR-515-5p, indicating the function of circRHBG/miR-515-5p/SLC7A11 axis in PCOS. Moreover, circRHBG silencing could promote ferroptosis in PCOS [23].

circMTO1 is another circRNA participating in the PCOS pathogenesis. Its knockdown has promoted proliferation of KGN and SVOG cells and suppressed their apoptosis rate. The effects of circMTO1 on these cells are mediated through miR-320b/MCL1 axis. Besides, circMTO1 expression in these cells has been stimulated by Snail family transcriptional repressor 2 (SNAI2) [24].

Expression of circASPH has also been found to be increased in PCOS patients, parallel with up-regulation of MAP2K6 and down-regulation of miR-375. This circRNA directly targets miR-375, which targets MAP2K6. Additionally, circASPH silencing represses proliferation of KGN cells and enhances their apoptosis [25]. circPUM1 is another circRNA that contributes to the development of PCOS via adsorbing miR-760 [26].

On the other hand, circPSMC3 expression has been shown to be abnormally reduced in the ovarian tissue of PCOS patients. Notably, up-regulation of this circRNA in PCOS model mice has relieved the symptoms. Moreover, circPSMC3 could inhibit cell proliferation and enhance apoptosis of OGCs through hindering cell cycle. These effects are mediated through miR-296-3p/PTEN axis [27].

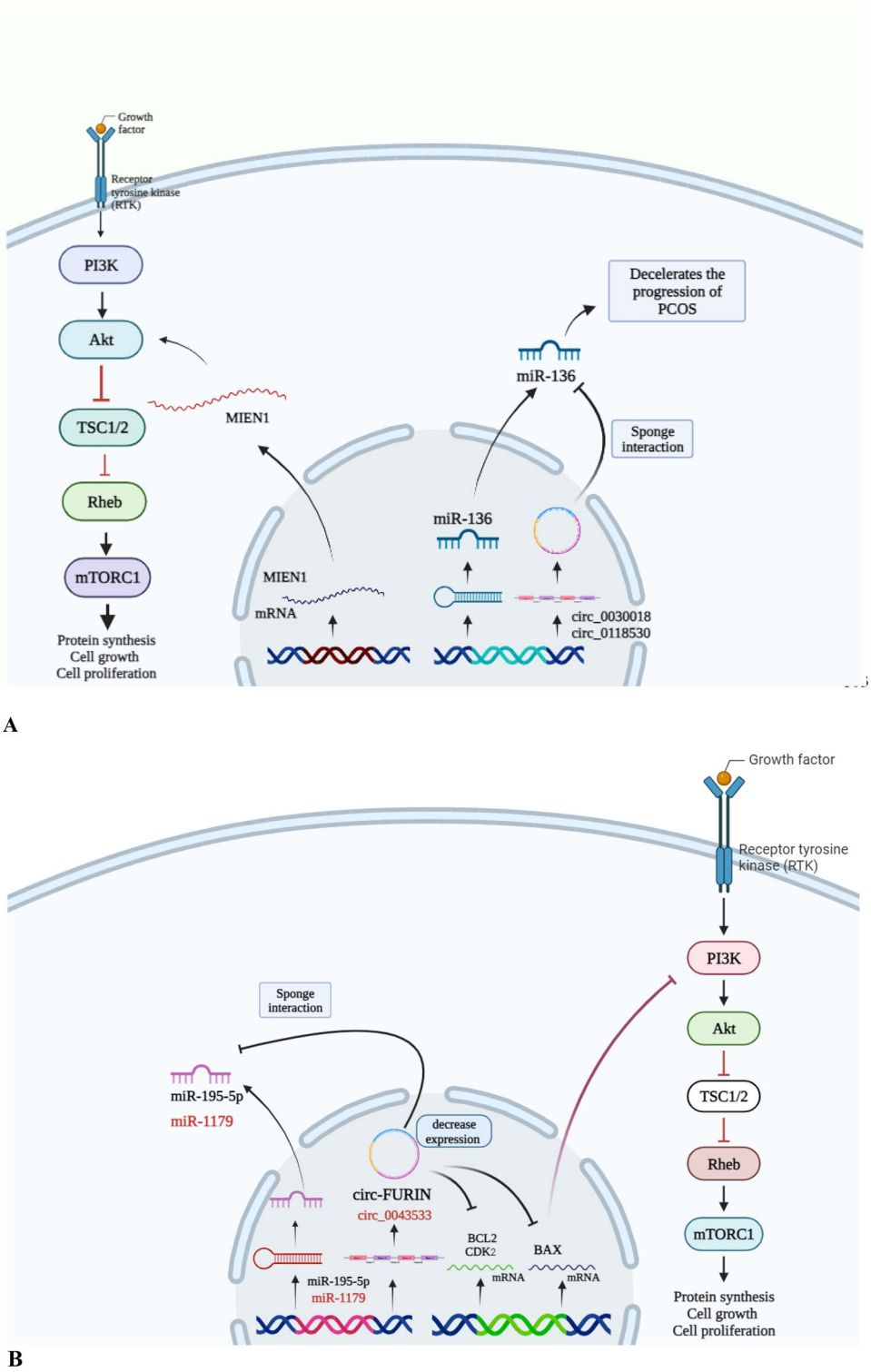

Fig. 1 **(A)** The mechanistic process underlying contribution of miR-136 in PCOS. hsa_circ_0118530 and circ_0030018 are two circRNAs that adsorb miR-136 in the context of PCOS. **(B)** The mechanism of involvement of circ_FURIN in the pathogenesis of PCOS

Expression profile of circRNAs has also been assessed in exosomes extracted from follicular fluid of PCOS patients versus controls [28]. Differentially expressed circRNAs have been predicted to contribute to the ovarian steroidogenesis, aldosterone biosynthesis and excretion, and Jak/STAT signaling. One of these circRNAs, namely hsa_circ_0006877 (circLDLR) has a prominent role in ovarian steroidogenesis. This circRNA has also been verified to be depleted in follicular fluid exosomes of additional PCOS cohort. The circLDLR/miR-1294/CYP19A1 ceRNA has been confirmed by functional studies in the cumulus cells of PCOS patients [28].

In addition, *in silico* studies have predicted some circRNA/miRNA axes in this condition. An example of this type of studies has been conducted by Huang et al. on three datasets of circRNAs, mRNAs and miRNAs, respectively [30]. Differentially expressed genes have been used to construct a network of cirRNA-related competing endogenous RNAs (ceRNAs). This study has validated dysregulation of three circRNAs, namely hsa_circ_0075691, hsa_circ_0075692 and hsa_circ_0085997 in PCOS. The constructed network included mentioned circRNAs as well as three miRNAs (hsa-miR-320c, hsa-miR-455-5p and hsa-miR-346) [30].

In addition to studies that have addressed function of circRNA/miRNA axes in PCOS, some other studies have evaluated expression levels of circRNAs in different tissues of PCOS patients. Most notably, maternal PCOS has been shown to affect expression of circRNAs in the fetus [31]. Zhao et al. have shown up-regulation of 14 circRNAs and down-regulation of 101 circRNAs in the fetal side of placenta from maternal PCOS compared with healthy puerperal through microarray analyses. Among differentially expressed circRNAs, expression profiles of circ_0023942, circ_0002151, circ_0001274, and circ_0008514 have been verified by qRT-PCR. Functional assay have shown that circ_0023942 represses proliferation of human OGCs and suppresses CDK-4 expression. Moreover, this circRNA has been predicted to participate in the regulation of developmental processes and MAPK signaling. Besides, circ_0023942 is predicted to target a number of miRNAs, namely hsa-miR-632, hsa-miR-574-3p, hsa-miR-362-5p, hsa-miR-429, and hsa-miR-502-5p [31].

An expression assay in cumulus cells of PCOS and non-PCOS subjects has shown up-regulation of 167 and down-regulation of 119 circRNAs. qRT-PCR experiments have validated up-regulation of hsa_circ_0043533 and hsa_circ_0043532; and down-regulation of hsa_circ_0097636 in the PCOS cases compared with non-PCOS ones. Levels of hsa_circ_0043533 and hsa_circ_0097636 in the PCOS cases have been correlated with testosterone levels. Most notably, differentially expressed circRNAs have been enriched in cell cycle, oocytes meiosis, progesterone-mediated oocytes maturation, FOXO and phosphatidylinositol signaling pathways as well as glycerophospholipids metabolism [32].

Bioinformatic analyses

In order to gain insight into the ceRNA network implicated in PCOS and offer a basis for further investigations, a number of *in-silico* analyses were conducted. Initially, we utilized the miRWalk database (http://mirwalk.umm.uni-heidelberg.de/) to identify the potential genes that are controlled by 13 miRNAs that have been thoroughly examined [33]. To ensure accuracy, we implemented a stringent criterion where the target genes must have a score higher than 0.95 and be predicted as target genes in all three datasets: TargetScan, miRDB, and miRTarbase. Our analysis revealed that a total of 80 unique genes have the potential to be regulated by 5 distinct miRNAs (Fig. 2A). Notably, previous research has focused solely on the investigation of BCL2 which is targeted by at least two miRNAs, namely has-miR-195-5p and has-miR-162-5p, as two important miRNAs in the pathoetiology of PCOS. The remaining 79 genes present an intriguing avenue for future studies. The Cytoscape version 3.10.1 was utilized to visualize the network of these interactions [34].

Subsequently, we utilized the miRNet version 2.0 database (https://www.mirnet.ca/miRNet/home.xhtml) to discover the upstream circRNAs that potentially control the expression or function of 13 miRNAs [35]. As illustrated in Fig. 2B, we observed that among them, only 11 miRNAs could be regulated by 6449 different circRNAs. Moreover, among these 11 miRNAs, five miRNAs were found in the previous step. These five miRNAs could be regulated by 5269 different circRNAs. Considering the published data and our *in-silico* analyses, it can be inferred that a ceRNA network comprising of 5269 circRNAs, 5 miRNAs, and 80 mRNAs potentially plays a role in the pathobiology of PCOS.

Finally, to identify the relevant pathway for these miRNAs, we employed the miRAnno module of the miRDIP version 5.3.0.1 database (https://ophid.utoronto.ca/mirDIP/miRAnno.jsp), a tool commonly utilized by researchers to investigate miRNA-associated pathways in Homo sapiens [36, 37]. As listed in Table 2, By importing the miRNA list, we discovered that out of the 13 miRNAs examined, 11 miRNAs were associated with a total of 35 distinct human pathways (P-value < 0.001).

Discussion

Epigenetic factors are involved in the pathogenesis of PCOS as well as the observed heterogeneity in the clinical manifestation and metabolic complications related with PCOS. Moreover, epigenetic inheritance of PCOS provides prospects for novel treatment options in this disorder [38]. CircRNAs have been shown to be involved in the pathogenesis of PCOS and related pathologies. The main mechanism through which they exert their functions is modulation of biological availability of miRNAs. However, the miRNAs sponged by dysregulated circRNAs in PCOS have not been identified completely. We reported several circRNA/miRNA axes that contributed to the pathoetiology of PCOS.

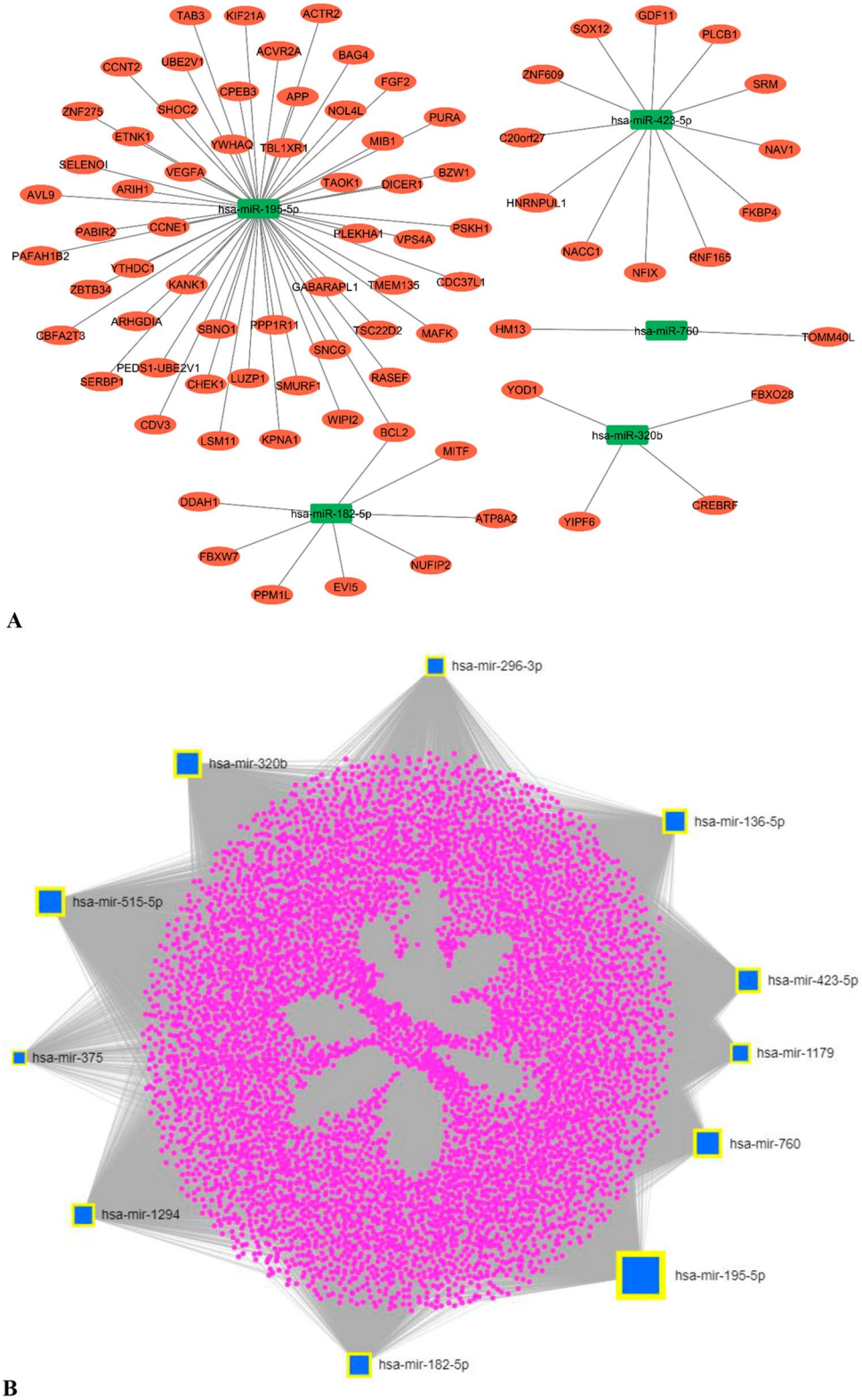

Fig. 2 (**A**) The possible miRNAs-mRNAs interaction network in PCOS, retrieved from the miRWalk database and visualized by the Cytoscape version 3.10.1. (**B**) The potential circRNAs-miRNAs interaction network in PCOS, obtained from the miRNet version 2.0 database and illustrated by the Cytoscape version 3.10.1

Among the reported miRNAs, miR-136 has been shown to be sponged by three circRNAs, namely circ_0030018 [18], circ_RANBP9 [19] and hsa_circ_0118530 [20] in the PCOS context. Thus, this miRNA has a prominent role in this process. The role of this miRNA in the pathogenesis of PCOS has also been evaluated by other studies. For instance, expression of miR-136-3p has been found to be elevated in rat ovaries and isolated OGCs following an ovulatory dose

Table 2 The possible miRNA-related pathways in PCOS.

Pathway	Affinity	Z	*P*-value
BioCarta:eukaryotic protein translation	1.87E-04	5.52426	1.65E-08
WikiPathways:Translation Factors	6.42E-04	4.60218	2.09E-06
Reactome:PKB-mediated events	1.29E-04	4.366403	6.32E-06
SIGNOR:Adipogenesis	9.78E-05	4.255751	1.04E-05
Reactome:Signal transduction by L1	4.88E-05	4.254517	1.05E-05
Reactome:mTOR signalling	1.25E-04	4.239218	1.12E-05
BioCarta:influence of ras and rho proteins on g1 to s transition	2.20E-05	4.142363	1.72E-05
Reactome:RNF mutants show enhanced WNT signaling and proliferation	3.85E-05	4.067436	2.38E-05
BioCarta:nerve growth factor pathway (ngf)	1.33E-05	4.021492	2.89E-05
Reactome:PI3K Cascade	1.62E-04	3.931467	4.22E-05
Reactome:Cellular responses to external stimuli	0.002395	3.914619	4.53E-05
BioCarta:endocytotic role of ndk phosphins and dynamin	1.29E-04	3.911869	4.58E-05
Reactome:Disinhibition of SNARE formation	2.41E-05	3.811495	6.91E-05
Reactome:Synthesis of Dolichyl-phosphate	7.07E-05	3.789407	7.55E-05
WikiPathways:miR-509-3p alteration of YAP1/ECM axis	2.06E-04	3.645637	1.33E-04
Reactome:Energy dependent regulation of mTOR by LKB1-AMPK	1.02E-04	3.64339	1.35E-04
Reactome:PRC2 methylates histones and DNA	2.22E-04	3.545747	1.96E-04
HumanCyc:dermatan sulfate biosynthesis	1.57E-04	3.480016	2.51E-04
PID:Nectin adhesion pathway	1.51E-04	3.462088	2.68E-04
EHMN:Proteoglycan biosynthesis	2.48E-04	3.395093	3.43E-04
BioCarta:role of ppar-gamma coactivators in obesity and thermogenesis	1.66E-05	3.391798	3.47E-04
Reactome:Cellular responses to stress	0.001614	3.387478	3.53E-04
Reactome:HATs acetylate histones	0.001633	3.38428	3.57E-04
Reactome:Golgi-to-ER retrograde transport	8.51E-04	3.372812	3.72E-04
Reactome:Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer's disease models	8.57E-05	3.356706	3.94E-04
Reactome:Neurodegenerative Diseases	8.57E-05	3.356706	3.94E-04
BioCarta:cyclin e destruction pathway	1.50E-05	3.311064	4.65E-04
PID:IL2 signaling events mediated by PI3K	6.27E-05	3.193219	7.03E-04
WikiPathways:Interactome of polycomb repressive complex 2 (PRC2)	8.18E-04	3.144204	8.33E-04
BioCarta:igf-1 signaling pathway	2.12E-05	3.121555	8.99E-04
Reactome:Axonal growth stimulation	1.42E-05	3.117806	9.11E-04
Reactome:Chromatin modifying enzymes	0.003654	3.11227	9.28E-04
Reactome:Chromatin organization	0.003654	3.11227	9.28E-04
BioCarta:pdgf signaling pathway	2.22E-05	3.108063	9.42E-04
WikiPathways:miRNAs involved in DNA damage response	2.39E-05	3.10242	9.60E-04

of LH-human chorionic gonadotropin (hCG). At the same time, transcript levels of the hCG receptor (LHR) have been decreased suggesting the effect of miR-136-3p in targeting LHR [39].

Besides, circ_FURIN has been shown to sponge both miR-423-5p [29] and miR-195-5p [21]. Taken together, a certain circRNA can sponge several miRNAs. Meanwhile, a miRNA can be targeted by several circRNAs. Thus, a complex network exists between these two types of transcripts in the context of PCOS.

In addition to circRNAs that regulate function of OGCs, exosomal circRNA can modulate follicular microenvironment and participate in the etiology of PCOS. Thus, future studies can use this biological source to find novel biomarkers for PCOS.

ceRNA axes that contribute to the pathogenesis of PCOS can affect a number of cellular processes, particularly cell apoptosis. Notably, OGCs apoptosis is involved in all phenotypes of PCOS; and suppression of OGCs apoptosis can assuage several clinical manifestations associated with PCOS [40]. Thus, modulation of activity of these molecular axes can be considered as a treatment modality for PCOS. In addition to apoptosis, another route of cell death, i.e. ferroptosis has been found to be affected by a circRNA, namely circRHBG in PCOS [23]. In line with this finding, involvement of ferroptosis-related genes in the pathophysiology of PCOS has been recently highlighted [41].

The mechanism by which expression of cicRNAs is induced in PCOS is not elucidated completely, However, a number of transcription factors such as SNAI2 might be involved in this process [24]. Additional underlying mechanisms and the effects of environmental factors should be investigated in future studies.

To understand the ceRNA network in PCOS, *in-silico* analyses were conducted using the miRWalk, miRNet, and miRDIP databases. We focused on understanding the role of circRNA/miRNA interactions in PCOS, but we started from dysregulated genes and miRNAs. The miRWalk database identified 80 unique genes potentially regulated by five miRNAs, while miRNet revealed 6449 circRNAs that could control the expression or function of 11 miRNAs. The miRAnno module of miRDIP identified 11 miRNAs associated with 35 human pathways. Among thee pathways are those related with protein translation, adipogenesis, mTOR signaling, WNT signaling, PI3K cascade, cellular responses to stress, chromatin organization and DNA damage response. These findings provide a foundation for further investigations into the role of the ceRNA network in PCOS.

Conclusion and future directions

Cumulatively, evidence discussed in the current literature review supports involvement of circRNAs in the pathophysiology of PCOS and its related pathologies. Of particular note, circRNA signature and the interaction between circRNAs and miRNAs can explain the pathological changes occurred in this condition and predict the response to treatment options for infertility. Moreover, these networks are components of epigenetic machinery that controls expression of genes and chromatin structure.

Finally, the epigenetic model consisted of ceRNA network is in favor of the proposed evolutionary model for PCOS pathogenesis. This synthesis of the available evidence is predicted to evolve over time. Thus, future studies would enhance the understanding of the pathobiology of PCOS and the relevance of environmental versus genetic factors in the modulation of this condition.

Author contributions M.A. designed the tables. M.F and A.M. designed figures. S.G-F wrote the manuscript. All authors reviewed the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval Not applicable.

Conflict of interest Authors declare no conflict of interest.

Competing interests The authors declare no competing interests.

References

1. Rasquin LI, Anastasopoulou C, Mayrin JV (2023) Polycystic ovarian disease. StatPearls. Treasure Island FL ineligible companies. Disclosure: Catherine Anastasopoulou declares no relevant financial relationships with ineligible companies. Disclosure: Jane Mayrin declares no relevant financial relationships with ineligible companies. © 2023. StatPearls Publishing LLC.
2. Parker J, O'Brien C, Hawrelak J, Gersh FL (2022) Polycystic ovary syndrome: an evolutionary adaptation to Lifestyle and the Environment. Int J Environ Res Public Health. ;19(3)
3. Cooper HE, Spellacy WN, Prem KA, Cohen WD (1968) Hereditary factors in the Stein-Leventhal syndrome. Am J Obstet Gynecol 100(3):371–387
4. Diamanti-Kandarakis E, Piperi C (2005) Genetics of polycystic ovary syndrome: searching for the way out of the labyrinth. Hum Reprod Update 11(6):631–643
5. Parker J (2020) Understanding the pathogenesis of polycystic ovary syndrome: transgenerational evolutionary adaptation to lifestyle and the environment. J Australasian Coll Nutritional Environ Med 39(4):18–26
6. Day F, Karaderi T, Jones MR, Meun C, He C, Drong A et al (2018) Large-scale genome-wide meta-analysis of polycystic ovary syndrome suggests shared genetic architecture for different diagnosis criteria. PLoS Genet 14(12):e1007813
7. Crespo RP, Bachega T, Mendonça BB, Gomes LG (2018) An update of genetic basis of PCOS pathogenesis. Archives Endocrinol Metabolism 62(3):352–361
8. Concha CF, Sir PT, Recabarren SE, Pérez BF (2017) [Epigenetics of polycystic ovary syndrome]. Rev Med Chil 145(7):907–915
9. Bose R, Ain R (2018) Regulation of transcription by circular RNAs. Adv Exp Med Biol 1087:81–94
10. Shao T, Pan YH, Xiong XD (2021) Circular RNA: an important player with multiple facets to regulate its parental gene expression. Mol Ther Nucleic Acids 23:369–376
11. Zaiou M (2020) The emerging role and promise of circular RNAs in obesity and related metabolic disorders. Cells. ;9(6)
12. Prasad M, Jayaraman S, Veeraraghavan VP (2022) An intriguing role of circular RNA in insulin resistance and endothelial dysfunction: the future perspectives. Hypertens Res 45(11):1843–1845
13. Yin W, Zhang Z, Xiao Z, Li X, Luo S, Zhou Z (2022) Circular RNAs in diabetes and its complications: current knowledge and future prospects. Front Genet 13:1006307
14. Derakhshan Z, Bahmanpour S, Alaee S, Fallahi J, Tabei SMB (2023) The role of circular RNAs in Male Infertility and Reproductive cancers: a narrative review. Iran J Med Sci
15. Gao Q, Wang T, Pan L, Qian C, Wang J, Xin Q et al (2021) Circular RNAs: novel potential regulators in embryogenesis, female infertility, and pregnancy-related diseases. J Cell Physiol 236(10):7223–7241
16. Cheng J, Huang J, Yuan S, Zhou S, Yan W, Shen W et al (2017) Circular RNA expression profiling of human granulosa cells during maternal aging reveals novel transcripts associated with assisted reproductive technology outcomes. PLoS ONE 12(6):e0177888
17. Chen AX, Jin RY, Zhou WM, Ye YJ, Lu JL, Ren YF et al (2022) CircRNA circ_0043533 facilitates cell growth in polycystic ovary syndrome by targeting miR-1179. Reprod Biol 22(2):100637
18. Xu J, Qu Q, Liu B, Shen L (2022) The circular RNA circ_0030018/miR-136/migration and invasion enhancer 1 (MIEN1) axis promotes the progression of polycystic ovary syndrome. Bioengineered 13(3):5999–6011
19. Lu X, Gao H, Zhu B, Lin G, Circular RNA (2021) circ_RANBP9 exacerbates polycystic ovary syndrome via microRNA-136-5p/XIAP axis. Bioengineered 12(1):6748–6758

20. Jia C, Wang S, Yin C, Liu L, Zhou L, Ma Y (2020) Loss of hsa_circ_0118530 inhibits human granulosa-like tumor cell line KGN cell injury by sponging miR-136. Gene 744:144591
21. Chen Y, Miao J, Lou G (2021) Knockdown of circ-FURIN suppresses the proliferation and induces apoptosis of granular cells in polycystic ovary syndrome via miR-195-5p/BCL2 axis. J Ovarian Res 14(1):156
22. Xu L, Xiong F, Bai Y, Xiao J, Zhang Y, Chen J et al (2021) Circ_0043532 regulates miR-182/SGK3 axis to promote granulosa cell progression in polycystic ovary syndrome. Reprod Biol Endocrinol 19(1):167
23. Zhang D, Yi S, Cai B, Wang Z, Chen M, Zheng Z et al (2021) Involvement of ferroptosis in the granulosa cells proliferation of PCOS through the circRHBG/miR-515/SLC7A11 axis. Ann Transl Med 9(16):1348
24. Duan J, Cai H, Huang Y, Shi L (2021) SNAI2-Induced CircMTO1 promotes cell proliferation and inhibits apoptosis through the miR-320b/MCL1 Axis in Human Granulosa-Like Tumor cells. Front Genet 12:689916
25. Wu G, Xia J, Yang Z, Chen Y, Jiang W, Yin T et al (2022) CircASPH promotes KGN cells proliferation through miR-375/MAP2K6 axis in polycystic ovary syndrome. J Cell Mol Med 26(6):1817–1825
26. Deng L, Chen Q, Xie J, Wei W, Hui H (2020) circPUM1 promotes polycystic ovary syndrome progression by sponging to miR-760. Gene 754:144903
27. Liu J, Ding J, Qu B, Liu J, Song X, Suo Q et al (2020) CircPSMC3 alleviates the symptoms of PCOS by sponging mir-296-3p and regulating PTEN expression. J Cell Mol Med 24(18):11001–11011
28. Huang X, Wu B, Chen M, Hong L, Kong P, Wei Z et al (2020) Depletion of exosomal circLDLR in follicle fluid derepresses miR-1294 function and inhibits estradiol production via CYP19A1 in polycystic ovary syndrome. Aging 12(15):15414–15435
29. Xu X, Guan R, Gong K, Xie H, Shi L (2022) Circ_FURIN knockdown assuages testosterone-induced human ovarian granulosa-like tumor cell disorders by sponging mir-423-5p to reduce MTM1 expression in polycystic ovary syndrome. Reprod Biol Endocrinol 20(1):32
30. Huang P, Du S, Lin Y, Huang Z, Li H, Chen G et al (2021) Identification of three potential circRNA biomarkers of polycystic ovary syndrome by bioinformatics analysis and validation. Int J Gen Med. :5959–5968
31. Zhao C, Zhou Y, Shen X, Gong M, Lu Y, Fang C et al (2020) Circular RNA expression profiling in the fetal side of placenta from maternal polycystic ovary syndrome and circ_0023942 inhibits the proliferation of human ovarian granulosa cell. Arch Gynecol Obstet 301(4):963–971
32. Ma Z, Zhao H, Zhang Y, Liu X, Hao C (2019) Novel circular RNA expression in the cumulus cells of patients with polycystic ovary syndrome. Arch Gynecol Obstet 299(6):1715–1725
33. Sticht C, De La Torre C, Parveen A, Gretz N (2018) miRWalk: an online resource for prediction of microRNA binding sites. PLoS ONE 13(10):e0206239
34. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D et al (2003) Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res 13(11):2498–2504
35. Chang L, Xia J (2022) MicroRNA regulatory network analysis using miRNet 2.0. Transcription Factor Regulatory Networks. Springer, pp 185–204
36. Tokar T, Pastrello C, Rossos AEM, Abovsky M, Hauschild A-C, Tsay M et al (2018) mirDIP 4.1—integrative database of human microRNA target predictions. Nucleic Acids Res 46(D1):D360–D70
37. Shirdel EA, Xie W, Mak TW, Jurisica I (2011) NAViGaTing the micronome–using multiple microRNA prediction databases to identify signalling pathway-associated microRNAs. PLoS ONE 6(2):e17429
38. Stener-Victorin E, Deng Q (2021) Epigenetic inheritance of polycystic ovary syndrome — challenges and opportunities for treatment. Nat Reviews Endocrinol 17(9):521–533
39. Kitahara Y, Nakamura K, Kogure K, Minegishi T (2013) Role of microRNA-136-3p on the expression of luteinizing hormone-human chorionic gonadotropin receptor mRNA in rat ovaries. Biol Reprod 89(5):114
40. Ding L, Gao F, Zhang M, Yan W, Tang R, Zhang C et al (2016) Higher PDCD4 expression is associated with obesity, insulin resistance, lipid metabolism disorders, and granulosa cell apoptosis in polycystic ovary syndrome. Fertil Steril 105(5):1330–1337e3
41. Lin S, Jin X, Gu H, Bi F (2023) Relationships of ferroptosis-related genes with the pathogenesis in polycystic ovary syndrome. Front Med 10:1120693