Non-coding RNA Research 9 (2024) 624–640

Contents lists available at ScienceDirect

Non-coding RNA Research

journal homepage: www.keaipublishing.com/en/journals/non-coding-rna-research

Review Article

Biomarker potential of competing endogenous RNA networks in Polycystic Ovary Syndrome (PCOS)

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ARTICLE INFO

Keywords:
Polycystic ovary syndrome
Competing endogenous RNA (ceRNA)
Long noncoding RNA
MicroRNAs
Circular RNAs
Regulatory networks

ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common condition affecting women of reproductive age globally. PCOS continues to be the largest contributing factor to female infertility despite significant progress in our knowledge of the molecular underpinnings and treatment of the condition. The fact that PCOS is a very diverse condition makes it one of the key reasons why we haven't been able to overcome it. Non-coding RNAs (ncRNAs) are implicated in the development of PCOS, according to growing evidence. However, it is unclear how the complex regulatory relationships between the many ncRNA types contribute to the growth of this malignancy. Competing endogenous RNA (ceRNA), a recently identified mechanism in the RNA world, suggests regulatory interactions between various RNAs, including long non-coding RNAs (lncRNAs), microRNAs (miRNAs), transcribed pseudogenes, and circular RNAs (circRNAs). Recent studies on PCOS have shown that dysregulation of multiple ceRNA networks (ceRNETs) between these ncRNAs plays crucial roles in developing the defining characteristics of PCOS development. And it is believed that such a finding may open a new door for a deeper comprehension of PCOS's unexplored facets. In addition, it may be able to provide fresh biomarkers and effective therapy targets for PCOS. This review will go over the body of information that exists about the primary roles of ceRNETs before highlighting the developing involvement of several newly found ceRNETs in a number of PCOS characteristics.

1. Introduction

PCOS, an endocrine and metabolic disorder, is estimated to affect 5–20% of women of reproductive age [1]. The current diagnostic criteria for PCOS are based on endocrinological and reproductive characteristics, including clinical and/or biochemical hyperandrogenism, exclusion of other adrenal, pituitary, or androgenic abnormalities, polycystic ovarian morphology, and anovulation [2]. PCOS is further classified into four subgroups distinguished by heterogeneous and complex morphological and molecular characteristics [3]. It exhibits a high level of intrinsic heterogeneity, encompassing its etiology, clinical presentation, and long-term prognosis [4]. Despite advancements in our understanding of the molecular and genetic aspects of PCOS, as well as progress in preventive, diagnostic, and therapeutic methods, PCOS remains a significant factor in female infertility. The primary challenge stems from the fact that, despite the wide range of pathological characteristics and clinical behaviors observed in PCOS, its exact underlying cause has yet to be fully identified. As a result, the exploration of network regulatory interactions and cross-talk among all RNAs encoded by the genome, especially noncoding RNAs (ncRNAs), has received relatively less attention in relation to the various subgroups of PCOS. This limited focus may be attributed to the predominant emphasis of PCOS research on investigating the aberrant mechanisms and actions of individual genes, employing a narrow perspective.

The completion of human genome sequencing in 2001 revealed that only 75% of the genome is capable of producing active and functional transcription products. Among these, approximately 2% are protein-coding transcripts, while the majority comprises noncoding RNAs (ncRNAs) such as transcribed pseudogenes, circRNAs, miRNAs, and long non-coding RNAs (lncRNAs) [5]. While considerable research efforts have focused on mRNAs and miRNAs, there remain numerous unanswered questions regarding the roles and functions of lncRNAs,

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https://doi.org/10.1016/j.ncrna.2024.01.002
Received 22 October 2023; Received in revised form 21 December 2023; Accepted 8 January 2024
Available online 17 January 2024

circRNAs, and transcribed pseudogenes [5]. A proposed unified theory suggests that miRNA response elements (MREs) serve as the fundamental units of a novel communication language, enabling messenger RNAs, transcribed pseudogenes, and long non-coding RNAs to interact with each other. This ceRNA activity is believed to give rise to a large-scale regulatory network across the transcriptome, facilitating the dissemination of functional genetic information within the human genome and playing a crucial role in the pathogenesis of heterogeneous syndromes [6].

Recent research on PCOS has shown that there is dysregulation of multiple competitive endogenous RNA networks (ceRNETs) that are made up of different types of noncoding RNAs (ncRNAs). This makes it harder to set clear criteria for different types of PCOS and fits with what the ceRNA theory predicts [7,8]. This supports the notion that ceRNETs play significant roles in PCOS development. Consequently, identifying the RNA signatures within ceRNETs that contribute to the diversity of PCOS may provide new insights into its pathogenesis as well as new opportunities for discovering specific biomarkers and potential therapeutic targets for PCOS subgroup identification and treatment. In our study, we will begin by presenting the available information on the different components of CERNETs. We will focus on elucidating the critical biological activities of these components, including lncRNAs, circRNAs, miRNAs, and messenger RNAs (mRNAs). Subsequently, we will discuss the implications of these findings. Furthermore, we will delve deeper into the recently discovered pivotal functions that distinct CERNETs play in the progression of PCOS.

2. Non-coding RNAs are structural elements of CERNETs

2.1. CircRNAs

CircRNAs represent a novel class of non-coding RNAs characterized by their circular structure. They can be categorized based on their origin: exonic circRNAs (ecircRNAs) formed by specific exons; circular intronic RNAs (ciRNAs) formed by intronic sequences; and exon-intron circRNAs that contain both intronic and exonic regions. CircRNAs may act as competing endogenous RNAs [9]. Unlike linear RNAs, circRNAs possess covalently closed RNA molecules without 5′ caps and 3′ tails, which confer stability within the cytoplasm. Their circular structure also makes them more resistant to degradation by exonucleases or RNases due to the lack of exposed 3′ and 5′ terminals (Fig. 1A). CircRNAs exhibit unique features such as the ability to code for proteins, evolutionary conservation, and tissue specificity [10]. These characteristics make them promising candidates for prognostic and diagnostic biomarkers in multifactorial disorders, syndromes, and cancers, depending on the specific tissue. CircRNAs have been detected in various sources, such as exosomes [11], follicular fluids [12], granulosa cells (GCs) [13], cumulus cells [14], and blood [15]. They have demonstrated potential as biomarkers in the diagnosis of various disorders, particularly multifactorial cancers and genetic disorders. CircRNAs exert their functions through diverse mechanisms, including acting as miRNA sponges, interacting with RNA-binding proteins (RBPs), regulating transcription, alternative splicing, and even producing functional peptides that contribute to the onset and development of diseases [16]. In recent years, circRNAs have gotten a lot of attention because there is more and more evidence that they play a key role in the progression and development of many types of cancer caused by functional problems [17]. New research has shown that the levels of novel circRNAs are much less stable in PCOS patients than in control groups. This suggests that they could be used as diagnostic and therapeutic targets. These dysregulated circRNAs act as sponges, inhibiting miRNAs and exerting post-transcriptional control over genes of interest. Several recent studies have shown how important dysregulated circRNAs are in the pathogenesis and clinical-pathological effects of PCOS. This shows how important they are as biomarkers for treatment and diagnosis [18].

2.2. miRNAs

The significance of miRNA roles is widely accepted, supported by a substantial body of evidence accumulated since their discovery [19,20]. Given that each miRNA is hypothesized to regulate a large number of targets, it is believed that they exert control over the majority of genes that code for proteins [21]. This implies that miRNA expression can influence almost every biological activity. The impressive evolutionary conservation observed in miRNAs and the proteins they regulate further supports their functional relevance [22,23]. Furthermore, it has been observed that individuals with mutations inhibiting miRNA processing [24,25] are not viable, indicating that a complete absence of miRNA activity is incompatible with life. Structurally, miRNAs are small single-stranded RNAs consisting of 20–25 nucleotides. They are endogenously expressed and play essential roles in cellular networks [26]. It is well established that miRNAs primarily target the 3′ untranslated regions (UTRs) of mRNAs [27], thereby blocking gene expression at the post-transcriptional level. Additionally, protein-coding sequences (CDS) have been identified as potential targets for miRNAs through miRNA recognition elements (MREs) [28]. MREs are present in various types of RNAs, including mRNAs, lncRNAs, and circRNAs, with a higher frequency in the 3′ UTRs compared to the 5′ UTRs [29]. These different types of RNA form a mutual regulatory network where they regulate each other's expression. Despite targeting different molecules, they share commonalities in terms of their overall function [30] (Fig. 1B).

Sardina et al. found that RNA transcripts with the same miRNA recognition elements (MREs) on their 3′ untranslated regions (UTRs) may be able to control each other's expression levels using a ceRNA mechanism [31]. The miRNA → RNAs regulatory model has been expanded to include a more comprehensive RNAs ↔ miRNAs ↔ RNAs interaction network, which forms the basis of the current unified theory on how different types of RNA communicate with each other using MREs as a language. It is important to note that each miRNA can target multiple RNAs, and each RNA can be targeted by multiple miRNAs, emphasizing the complexity and versatility of the ceRNA regulatory networks. Even a small subset of miRNAs and associated transcripts has the potential to generate highly intricate and interconnected ceRNETs [6]. Numerous studies have linked altered miRNA levels to the development of various disorders, including complex genetic diseases including neurodegenerative diseases [32,33], cancer [34], and metabolic and hormonal diseases such as PCOS [35]. Specifically, abnormal miRNA expression has been implicated in the pathogenesis and progression of PCOS, with evidence suggesting its involvement in peripheral blood leukocytes, serum, follicular fluid, adipose tissue, theca cells, and GCs [35]. These findings highlight the significance of miRNA dysregulation in PCOS processes and underscore the potential diagnostic and therapeutic implications of targeting miRNAs in the context of this syndrome.

2.3. LncRNAs

Non-coding transcripts encompass a wide range of RNA molecules, with some being small in size while the majority are lncRNAs that exceed 200 nucleotides in length. RNA polymerase II is primarily responsible for transcribing lncRNAs, which results in the addition of a polyadenylated tail at their 3′ ends and a cap at their 5′ ends (Fig. 1C). The human genome is estimated to encode around 16,000 genes, which give rise to over 28,000 distinct lncRNA transcripts [36]. LncRNAs exhibit diverse functions depending on their specific characteristics. They can act as sponges for other RNAs, decoys, scaffolds, guides, or signaling molecules, thereby exerting regulatory control over gene expression at various levels, including translation, post-transcriptional processing, transcriptional regulation, and epigenetic modifications [37]. With their multifaceted effects, lncRNAs are often referred to as the "master regulators" of the genome [37]. Dysregulation of lncRNA genes has been implicated in numerous human disorders [38,39],

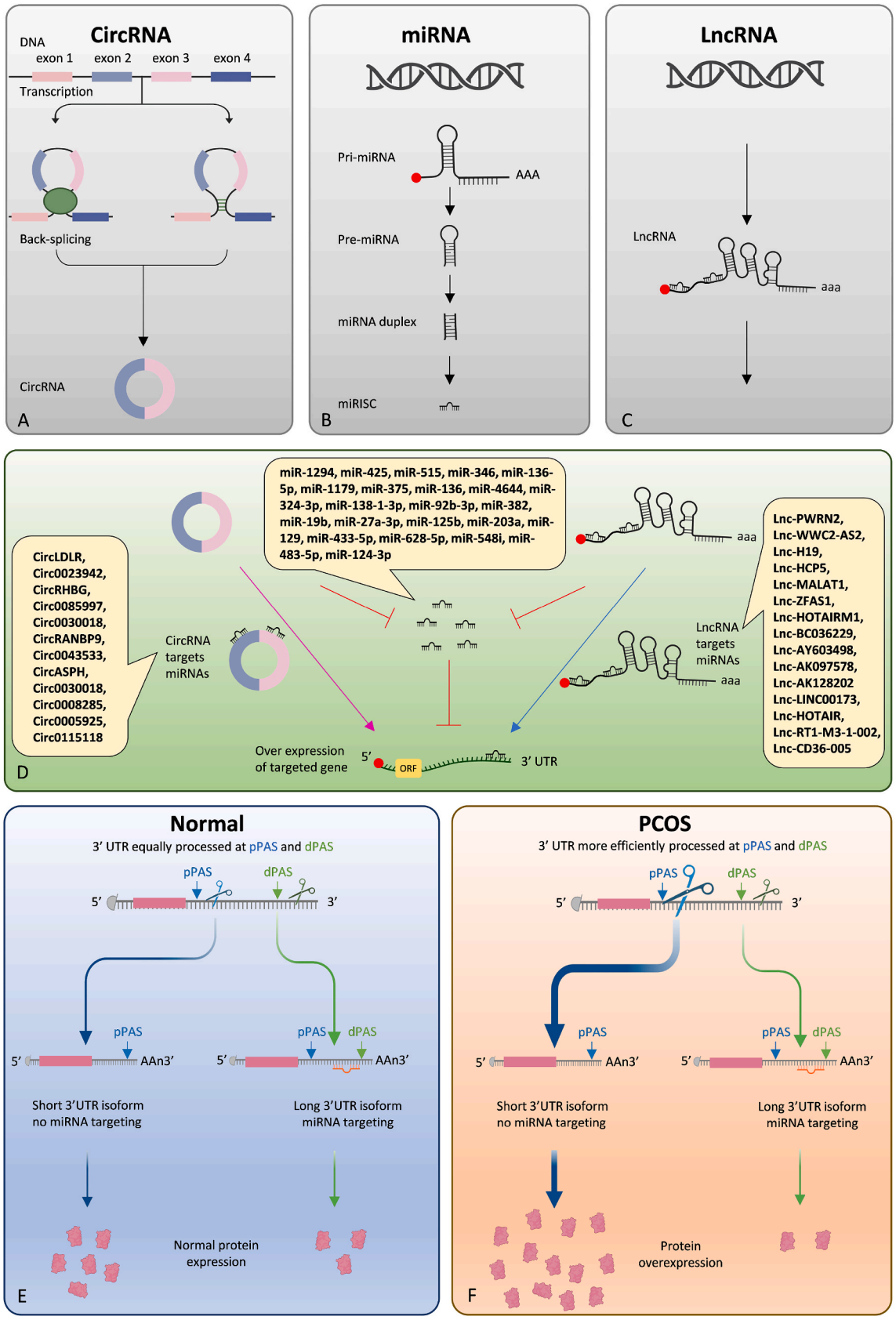

Fig. 1. Non-coding RNA Biogenesis and Regulatory Functions in ceRNETs. The figure provides an overview of the biogenesis and regulatory functions of ncRNAs within ceRNETs. A: CircRNAs, B: miRNAs, and C: lncRNAs are highlighted as key types of ncRNAs involved in gene regulation. These ncRNAs participate in the competitive binding mechanism with mRNAs, leading to regulatory interactions within ceRNETs. D: The figure illustrates the interplay between lncRNAs and circRNAs with miRNAs in competitive endogenous axes in the context of polycystic ovarian syndrome (PCOS). E: Different isoform with equally processed 3′ UTR isoform lengths. F: Different isoforms efficiently processed into short isoforms can have implications for microRNA (miRNA) targeting.

including polycystic ovarian syndrome (PCOS) [40]. Abnormal expression levels, absence, or mutations of lncRNAs have been associated with PCOS pathology [40]. For instance, analysis of RNA sequencing data from women with and without PCOS has revealed differential expression of lncRNAs in peripheral blood leukocytes [41], serum [42], follicular fluid [43], adipose tissue [44], and GCs [45]. Particularly, lncRNAs involved in ceRNETs and their dysregulation have been linked to PCOS [46]. The dysregulation of lncRNAs makes the molecular processes that cause PCOS even more complicated and shows how important it is to study these noncoding transcripts to fully understand the disease. More research into the specific roles and ways that lncRNAs are controlled in PCOS and other diseases could lead to the discovery of new diagnostic markers and treatment targets.

3. Proven and potential study of novel CERNETs in PCOS

Fig. 1D–F shows how important RNA cross-talks in recently found ceRNA regulatory networks are as biomarkers for PCOS. These cross-talks affect the post-translational levels of molecular processes that happen after translation.

3.1. CircRNA, miRNA, and mRNA in ceRNETs

In 2019, researchers began looking into the link between circRNAs and PCOS. Their main focus is on the role of circRNAs in granulosa cells and how they affect oocyte development. However, there remains a paucity of studies exploring abnormalities in the endometria of women diagnosed with PCOS. In this study, we conducted a comprehensive comparative study on cross-talk between circRNAs in various tissues in women with and without PCOS, aiming to explain the most prominent ceRNETs and shed light on their potential implications in the context of PCOS.

3.1.1. CircLDLR/miR-1294/CYP19A1

In 2020, Huang et al. confirmed the existence of a significant ceRNET involving circLDLR, miR-1294, and CYP19A1 in the steroidogenesis pathway [47]. CircLDLR is generated through a back-splicing mechanism from *LDLR* [57], a cell membrane protein that plays a crucial role in steroid biosynthesis and modulates coronary artery disease [58]. Elevated levels of circLDLR have been shown to increase cholesterol levels and promote cell proliferation and migration in colorectal cancer (CRC) cells [59]. MiR-1294 has been implicated in promoting PCOS by contributing to obesity and insulin resistance in polycystic ovarian syndrome [60], while showing potential benefits in ameliorating OC [61]. In our previous study, we emphasized *CYP19A1* as a potential biomarker crucial for the conversion of testosterone to estradiol during steroidogenesis [62]. The reciprocal activities of circLDLR and miR-1294 in the ceRNETs are believed to contribute to PCOS development. The CircLDLR/miR-1294/*CYP19A1* axis holds promise as a prognostic biomarker and therapeutic target for PCOS. These findings shed light on the management of PCOS at the system level.

3.1.2. Circ_0023942/miR-425/CDK4

In 2020, Zhao et al. published a ceRNA axis in ovarian GCs that was made up of circ_0023942, miR-425, and CDK4. According to the ceRNA theory, circ_0023942 competes with miR-425 to bind to CDK4. Functionally, circ_0023942 negatively regulates miR-425 while positively regulating CDK4. The relative expression of circ_0023942 is decreased in PCOS OGCs, which in turn leads to reduced KGN cell proliferation. The opposite trend is observed when the circ_0023942 expression is increased. Circ_0023942 plays a role in controlling the MAPK signaling pathway and developmental processes [48]. MiR-425 has been shown to modulate PBC inflammation through upregulation of N-Ras [63] and acts as an oncogene by targeting SMAD2 in SCC [64]. CDK4 functions as a modulator of the cell cycle [65] and has implications for cancer therapy [66]. However, CDK4 exhibits inhibitory effects in breast cancer (BRCA) [67]. Therefore, a regulatory loop involving circ_0023942, miR-425, and CDK4 is established in the context of PCOS development. Understanding this ceRNET's impact on OGC proliferation and cell cycle regulation in PCOS could be valuable for the identification of potential therapeutic and diagnostic targets for the condition.

3.1.3. CircRHBG/miR-515/SLC7A11

In 2021, Zhang et al. observed the involvement of the circRHBG, miR-515 and SLC7A11 ceRNET in PCOS. It was demonstrated that CircRHBG competes with miR-515 for binding to SLC7A11. Mechanistically, circRHBG acts as a sponge for miR-515, positively regulating the expression of SLC7A11 while negatively modulating miR-515. Elevated expression of circRHBG was observed in PCOS, KGN, and SVOG cells, promoting cell proliferation. Conversely, downregulation of circRHBG in PCOS facilitates ferroptosis through the circRHBG/miR-515/SLC7A11 axis [49]. There is a positive correlation between serum free testosterone levels in PCOS patients and miR-155 [68,69]. Additionally, miR-515-5p has been shown to regulate MARK4, governing the migration of cancer cells [70]. Through the miR-515-5p/GINS2 axis, lnc-SNHG3 promotes the growth and metastasis of bladder cancer [71], while it acts as a tumor suppressor in PC [72]. SLC7A11 is involved in iron-dependent cell death processes [73], and it has been implicated in tumor promotion [74], and oral squamous cell carcinoma [75]. The circRHBG/miR-515/SLC7A11 axis is believed to play a role in PCOS. These current insights may contribute to the clinical diagnosis and management of PCOS.

3.1.4. Circ_0085997/miR-346/PRICKLE2

In 2021, Huang et al. identified a novel ceRNET involving circ-0085997, miR-346, and *PRICKLE2*. Their study revealed that circ_0085997 competes with miR-346 to target *PRICKLE2*. Functionally, circ_0085997 positively regulates the expression of *PRICKLE2* while negatively modulating miR-346. Specifically, in GCs, the down-regulation of circ_0085997 leads to PRICKLE2 inhibition, whereas upregulation of miR-346 occurs. This regulatory mechanism involving the circRNA promotes the miR-346/PRICKLE2 axis, which influences the inflammatory response during the development of polycystic ovary syndrome (PCOS) [50]. MiR-346 appears to be crucial in ER-stress-induced autophagy [76], and it promotes the LIF/STAT3 signaling pathway in Hu sheep ovarian GCs [77]. Moreover, miR-346 sponging by circRNA promotes HCC [78] and CRC proliferation and migration through the miR-346/NFIB axis [79]. Overexpression of PRICKLE2 has been shown to promote neurodevelopmental delay and cognitive impairment [80]. The involvement of the circ_0085997/miR-346/PRICKLE2 axis, as well as Cyclin D1, in PCOS may be elucidated by the available data, providing insights into the diagnostic and therapeutic potential of ceRNETs.

3.1.5. Circ_RANBP9/miR-136-5p/XIAP

In 2021, Lu et al. first reported a novel ceRNETs involving circ_RANBP9, miR-136-5p, and *XIAP*. According to this network, circ_RANBP9 competes with miR-136-5p to bind to *XIAP*. Functionally, circ_RANBP9 positively regulates *XIAP* expression while negatively controlling miR-136-5p [51]. Increased levels of circ_RANBP9 were observed in the plasma of PCOS patients as well as in ovarian GCs. Depletion of circ_RANBP9 led to decreased development and enhanced apoptosis in KGN and COV434 cells, while miR-136-5p exerted opposite effects [51]. Interestingly, no previous PCOS studies have investigated circ_RANBP9, which encodes RANBP9, a scaffolding protein found in the cytoplasm and nucleus [81]. However, has-circ-0001577 has been identified as a potential circRNA in CRC cell proliferation [82]. MiR-136 has been implicated in regulating PCOS and KGN cells [54], and the miR-136-5p/*PBX3* axis has been shown to promote pancreatic cancer (PaCa) [83]. *XIAP*, a key regulator of cell growth and signaling pathways [84], is expressed in the ovary, particularly in thecal and GCs [85], and its overexpression has been observed in PCOS [84]. The

circ_RANBP9/miR-136-5p/*XIAP* axis holds potential as a predictive biomarker and therapeutic target for PCOS. These findings contribute to our understanding of the underlying mechanisms involved in the management of PCOS.

3.1.6. Circ_0043533/miR-1179/Bcl-2, CDK2, and Cyclin D1

In 2022, Chen et al. verified the existence of a ceRNET involving Circ-0043533, miR-1179, and the *Bcl-2*, *CDK2*, and *Cyclin D1* axis. Circ_0043533 competes with miR-1179 for binding to *Bcl-2*, *CDK2*, and *Cyclin D1*, thereby exerting regulatory control. Specifically, circ_0043533 positively regulates the expression of *Bcl-2*, *CDK2*, and *Cyclin D1*, while negatively regulating miR-1179 in OGCs and KGN cells. This regulatory mechanism impacts cell proliferation and apoptosis [52]. MiR-1179 has been demonstrated to suppress *NUAK2* expression, thereby inhibiting hepatocellular carcinoma (HCC) cell proliferation, migration, and invasion [86]. Additionally, by targeting *HMGB1*, miR-1179 reduces the proliferation of gastric cancer cells [87]. Furthermore, Circ-UBR5 has been found to promote UBR5 upregulation and malignancy in triple-negative BRCA through its interaction with miR-1179 [88]. *Bcl-2* plays a crucial role in antiapoptotic functions [89], while *CDK1* is involved in the regulation of the cellular cycle [90]. *CDK2* also plays significant roles in various biological functions [91]. Collectively, these findings suggest the involvement of the Circ_0043533/-miR-1179/*Bcl-2*, *CDK2*, and *Cyclin D1* axis in PCOS. This ceRNA axis could potentially serve as a diagnostic and therapeutic target for PCOS.

3.1.7. CircASPH/miR-375/MAP2K6

In 2022, Wu et al. confirmed the existence of a significant ceRNET involving CircASPH/miR-375/*MAP2K6*. It was found that CircASPH competes with miR-375 for binding to *MAP2K6*. CircASPH positively regulates the expression of *MAP2K6* while negatively modulates miR-375, and vice versa. Targeting of *MAP2K6* by CircASPH promotes KGN cell proliferation and inhibits apoptosis [53]. MiR-375 has been shown to induce KGN cell proliferation while promoting apoptosis [53]. Additionally, miR-375 targets *ADAMTS1* and *PGR* in bovine cumulus cells, thereby influencing the maturation of oocytes in vitro [92]. In bovine cumulus cells, miR-375 inhibits cell proliferation by targeting *JAK2* [93]. Furthermore, dysregulation of the miR-375/*JAK2* axis has been implicated in HCC [94], and is considered a prognostic biomarker in prostate cancer (PC) [95]. *MAP2K6* plays a key role in chromatin remodeling [96] and has been associated with the development of PCOS [97] and ovarian cancer [98]. These findings hold potential implications for the clinical diagnosis and therapy of PCOS, as the CircASPH/-miR-375/*MAP2K6* axis appears to be involved in the development of this condition.

3.1.8. Circ_0030018/miR-136/MIEN1

In 2022, Xu et al. confirmed the regulatory axis involving circ_0030018, miR-136, and *MIEN1*. Circ_0030018 competes with miR-136 to regulate *MIEN1* expression, positively regulating *MIEN1* while negatively regulating miR-136. Increased expression of circ_0030018 was observed in KGN cells and in individuals with PCOS. Deletion of circ_0030018 prevented the development of PCOS through the miR-136/*MIEN1* axis. Furthermore, downregulation of miR-136 reversed the effects of circ_0030018 silencing, while overexpression of *MIEN1* counteracted the impact induced by miR-136 in KGN cells [54]. Circ_0030018 has been reported to modulate *ENAH* expression by acting as a sponge for miR-599, exacerbating esophageal carcinoma [99], and promoting the growth and metastasis of glioma cells [100]. Targeting the miR-136/*NOTCH3* axis has been shown to promote endometrial cancer [101], while miR-136 targets *AEG-1* and *Bcl-2* to induce apoptosis in glioma cells [102]. *MIEN1* has been implicated in increasing oral cancer and decreasing survival rates [103], as well as promoting gastric cancer growth and metastasis through its upregulation [104]. These findings emphasize the diagnostic and therapeutic potential of the ceRNA regulatory network in PCOS. Understanding the circ_0030018/miR-136/*MIEN1* axis provides valuable insights into the underlying mechanisms involved in PCOS pathogenesis.

3.1.9. Circ_0008285/miR-4644/LDLR

In 2023, Yu et al. confirmed the role of circ_0008285/miR-4644/*LDLR* as ceRNET in PCOS. Circ_0008285 is a key circRNA that was retrieved from follicular exosomes and sponge miR-4644 and positively regulates *LDLR* expression. In KGN cell that treated with PCOS follicular exosomes the expression of circ_0008285 sponge miR-4644 which is directly regulate the expression level of *LDLR* in lipid metabolism pathway. Moreover, downregulated miR-4644 repress the expression of *LDLR* in normal cell [12]. Previously, data confirmed the increased plasma expression level of circ_0008285 in gestational diabetes [105]. In line with this, circ_0008285 promotes cervical cancer progression by targeting SOX4 [106]. However, in patients with colorectal cancer, circ0008285 acts as a tumor suppressor, and its expression is inversely correlated with lymph node metastases and tumor size [107]. Interestingly the miR-4644 expression level in serum and saliva exosomes significantly higher in PaCa compare to normal [108]. The miR-4644 downregulation might promote the growth and migration of melanoma cells, indicating that miR-4644 could function as a tumor suppressor in melanoma [109]. This is consist with Xin Huang results, which confirmed depleting *circLDLR* in exosomes increased the expression of miR-1294 and lowered the expression of *CYP19A1* in recipient cells [47]. It has been shown that the *LDLR* is crucial for lipoprotein metabolism, and overexpression of *LDLR* mRNAs in PCOS disrupts lipid homeostasis [110].

3.1.10. Circ_0005925/miR-324-3p/MAP2K6

In 2023, Yan et al. confirmed the role of circ_0005925/miR-324-3p/*MAP2K6* as ceRNET in PCOS. The circ_0005925 positively regulates *MAP2K6* expression level in GCs and sponge miR-324-3p and negatively controls its expression. miR-324-3p targets *MAP2K6* in knockdown circ_0005925, which leads to an increase in GC apoptosis concurrent with a decrease in proliferation [55]. Circ_0005925 originates from the *PILRB* gene. Zhang et al. (2019) reported that circ_0005925 exhibited significantly elevated expression levels in GCs derived from individuals with PCOS in comparison to those from healthy controls [13]. According to Jiang and Ma [111], research on PCOS revealed that the expression of miR-324-3p was decreased in the ovarian tissues of PCOS-model rats. In addition, it was discovered that miR-324-3p inhibited the proliferation of GCs. In addition, it has been shown that miR-324-3p is downregulated in goats with poor reproductive performance and inhibits the proliferation of goat GCs [112]. The results of this investigation suggest that miR-324-3p may inhibit the progression of PCOS. Several varieties of cancer, including esophageal adenocarcinoma [113] and osteosarcoma [114], have demonstrated that *MAP2K6* promotes cancer cell proliferation and accelerates cancer progression. Tang et al. [115] found that *MAP2K6* promotes neuron cell proliferation. Recent evidence suggests that circASPH functions as a sponge for miR-375, causing the upregulation of *MAP2K6*. This results in increased cell proliferation and decreased apoptosis in gastric cancer cells [53]. These findings lend support to the notion that circ_0005925/miR-324-3p/*MAP2K6* may play a role in the promotion of PCOS development.

3.1.11. Circ_0115118/miR-138-1-3p/WDFY2

In 2023, Yang et al. confirmed the role of circ_0115118/miR-138-1-3p/*WDFY2* as ceRNET in PCOS. The circ_0115118 mechanistically regulates *WDFY2* expression level in endometrial stromal cells (ESC) and sponge miR-138-1-3p and negatively controls its expression. miR-324-3p targets *WDFY2* in knockdown circ_0115118, which leads to an increase in endometrial stromal cells (ESC) apoptosis concurrent with a decrease in proliferation [56]. Circ_0115118 has not been extensively investigated thus far. Nevertheless, it has been observed that the expression of circ_0115118 is notably elevated in endometrial stromal cells during the proliferative phase in individuals with PCOS [56]. This

heightened expression is associated with the suppression of cellular mobilization and hindered embryo implantation. Studies on miR-138-1-3p now mostly concentrate on cancer cells. MiR-138-1-3p has been shown to decrease BEAS-2B cell motility and sponge 3-phosphoinositidedependent protein kinase 1 (*PDK1*), inhibiting malignant transformation [116]. MiR-138-1-3p was discovered to interact with CRIPTO in nasopharyngeal cancer, inactivating the JAK2/STAT3 pathway and rendering the radioresistant C666-IR and HK-1R NPC cell lines susceptible to radiation by preventing epithelial-mesenchymal transition [117]. *WDFY2*, has an unknown function [118]. *WDFY2* regulates downstream genes through *AKT* and protein kinase C [119, 120]. *WDFY2* inhibited prostate cancer cell colony formation and migration via the *AKT* pathway. *WDFY2* was downregulated in most malignancies, including BRCA, kidney renal papillary cell carcinoma (KICH), ovarian cancer (OV), and uterine carcinosarcoma (UCS), but increased in a few, showing its function in pan-cancer. In colon adenocarcinomas (COAD), rectum adenocarcinoma (READ), and sarcoma (SARC), increased *WDFY2* expression is associated with poorer disease outcomes in prognostic analyses, suggesting its oncogenetic involvement. The findings showed *WDFY2's* complicated role in malignancies [121] (Table 1 & Fig. 2).

3.2. LncRNA, miRNA, mRNA ceRNETs in PCOS

The investigation into the correlation between lncRNAs and PCOS was initiated in 2018, with a primary emphasis on examining the function of lncRNAs in granulosa cells and their participation in oocyte development. Nevertheless, there is a lack of research investigating irregularities in the endometria of women who have been diagnosed with PCOS. This study aimed to conduct a comprehensive comparative analysis on the cross talk between lncRNAs in women with and without PCOS. The objective was to elucidate the most prominent ceRNETs and provide insights into their potential implications in the context of PCOS.

3.2.1. PWNR2/miR-92b-3p/TMEM120B

In 2018, Huang et al. discovered a critical ceRNET involving lncRNA-PWRN2/miR-92b-3p/*TMEM120B*. They found that PWRN2 competes with miR-92b-3p for binding to *TMEM120B*, consistent with the ceRNA theory. LncRNA- PWRN2 acts as a sponge for miR-92b-3p, positively regulating *TMEM120B* expression. Overexpression of *TMEM120B* is associated with increased PCOS risk, obesity, adipocyte metabolism, and differentiation. Severe obesity is linked to spindle defects and misaligned chromosomes in infertile oocytes [122]. Additionally,

Table 1
CircRNAs, miRNAs, mRNAs ceRNETs in PCOS.

Organism	CeRNETs	Regulator		Inhibited		Targeted		Remarkable pathogenicity	Functional validation	Cell lines	Refs
Human	circRNA, miRNA, mRNA	CircLDLR	P ↓ N ↑	miR-1294	P ↑ N ↓	*CYP19A1*	P ↓ N ↑	↓ OS ↑ OS	Dual-luciferase reporter assay	GCs, KGN	[47]
		Circ_0023942	P ↑ N ↓	miR-425	P ↓ N ↑	*CDK4*	P ↑ N ↓	↓ CP ↑ CP	RT-Q-PCR	GCs, KGN, COV434	[48]
		CircRHBG	P ↑ N ↓	miR-515	P ↓ N ↑	*SLC7A11*	P ↑ N ↓	↓ CP, ↑ F ↑ CP, ↓ F	Dual-luciferase reporter assay	KGN, SVOG	[49]
		Circ_0085997	P ↓ N ↑	miR-346	P ↑ N ↓	*PRICKLE2*	P ↓ N ↑	↑ IR ↓ IR	Not validated	GCs	[50]
		Circ_RANBP9	P ↑ N ↓	miR-136-5p	P ↓ N ↑	*XIAP*	P ↑ N ↓	↑ CP, ↓ Ap ↓ CP, ↑ Ap	Dual-luciferase reporter assay	KGN, COV434, IOSE80	[51]
		Circ_0043533	P ↑ N ↓	miR-1179	P ↓ N ↑	*Bcl-2, CDK2, Cyclin D1*	P ↑ N ↓	↓ CP, ↑ Ap ↑ CP, ↓ Ap	Dual-luciferase reporter assay	GC, COV434, KGN	[52]
		CircASPH	P ↑ N ↓	miR-375	P ↓ N ↑	*MAP2K6*	P ↑ N ↓	↑ CP, ↓ Ap ↓ CP, ↑ Ap	Dual-luciferase reporter assay	KGN, SVOG	[53]
		Circ_0030018	P ↓ N ↑	miR-136	P ↑ N ↓	*MIEN1*	P ↓ N ↑	↓ CP, ↑ Ap ↑ CP, ↓ Ap	Dual-luciferase reporter assay	KGN	[54]
		Circ_0008285	P ↑ N ↓	miR-4644	P ↓ N ↑	*LDLR*	P ↑ N ↓	↑ lipid metabolism ↓ lipid metabolism	Dual-luciferase reporter assay	KGN	[12]
		Circ_0005925	P ↑ N ↓	miR-324-3p	P ↓ N ↑	*MAP2K6*	P ↑ N ↓	↑ CP, ↓ Ap ↓ CP, ↑ Ap	Dual-luciferase reporter assay	KGN	[55]
		Circ_0115118	P ↑ N ↓	miR-138-1-3p	P ↓ N ↑	*WDEY2*	P ↑ N ↓	↑ CP, ↓ Ap ↓ CP, ↑ Ap	Dual-luciferase reporter assay	–	[56]

Apoptosis (Ap), Competitive endogenous RNA Networks (CeRNETs), Cell proliferation (CP), Ferroptosis (F), Granulosa cell (GC), Human granulosa-like tumor cell line (KGN), Human ovarian surface epithelial cells (IOSE80), Immortalized granulosa cells (COV434), Immortalized human granulosa cells (SOVG), Normal (N), Ovarian Steroidogenesis (OS), Patient (P).

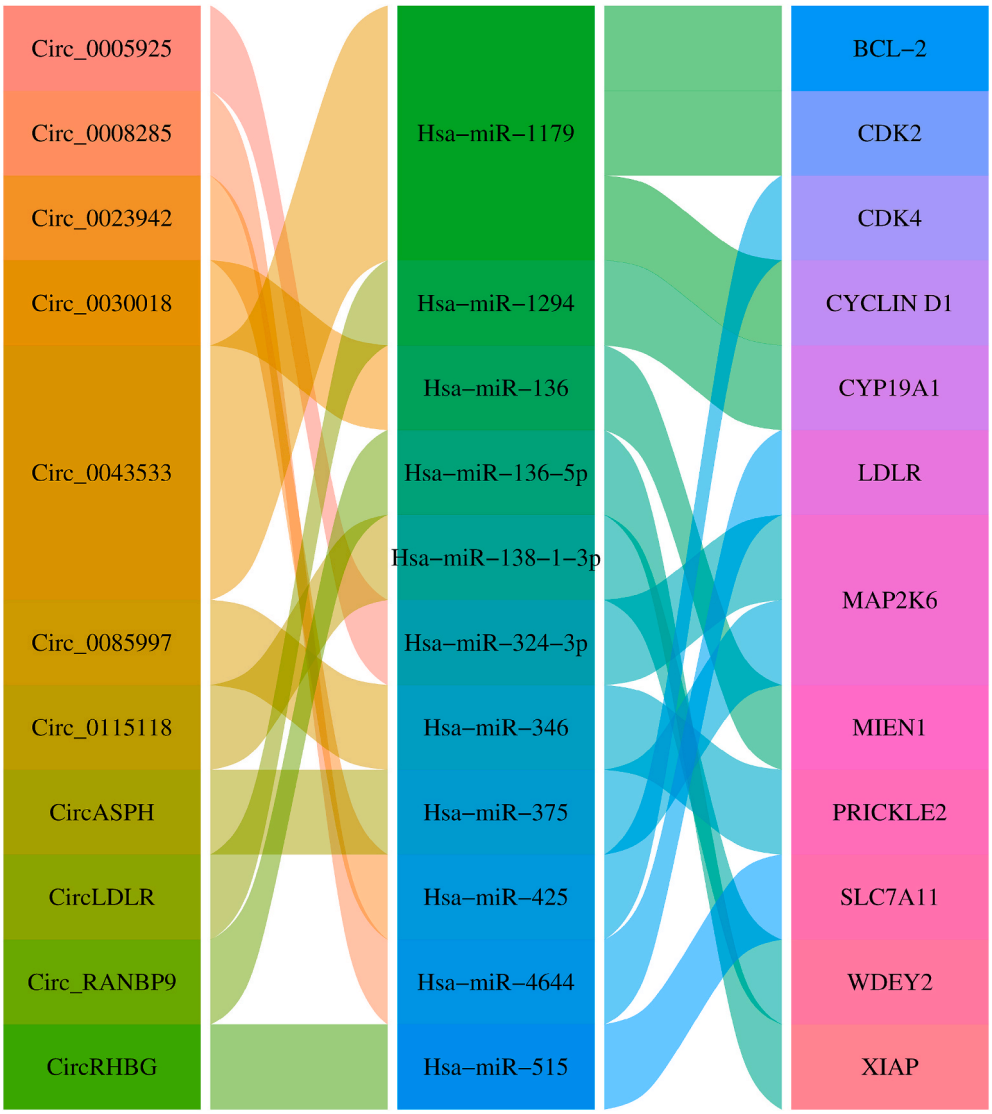

Fig. 2. The alluvial plot ceRNA construction of competitive endogenous RNA networks in women with PCOS. The left column represents circRNAs, the center column represents miRNAs, and the right column represents mRNAs. Stream blocks between the columns represent correlation between axes.

miR-92b-3p has been shown to target *TSC1* in neonatal mouse ovaries, controlling primordial follicle assembly [123], and inhibiting *FBXW7* to promote CRC cell proliferation, invasion, and migration [124]. Moreover, miR-92b-3p targets *GABRA3* to inhibit PaCa proliferation [125], while *TMEM120B* encodes a transmembrane protein that regulates adipose tissue metabolism [126], and contributes to oocyte nuclear maturation [126]. These results contribute to our understanding of the PWRN2/miR-92b-3p/*TMEM120B* ceRNA regulatory network in PCOS development, highlighting its diagnostic and therapeutic potential.

3.2.2. *WWC2-AS2/miR-382/PLCG2*

Evidence recently obtained during an inquiry, in 2020 a crucial ceRNAs network WWC2-AS2/miR-382/*PLCG2* disclosed by Zeng et al., WWC2-AS2 positively regulates *PLCG2*, and negatively regulates miR-382, and vice versa, targeted *PLCG2* influencing development of PCOS with promotion of immune response, and cell proliferation [127]. In supports with lncRNA WWC2-AS2 has potential as a prognosis biomarker in lung adenocarcinoma [128], modulates *BRCA* cell proliferation [129]. MiR-382-5p has a negative correlation with a free androgen level [130], down-regulating miR-382-5p through *FZD3* sponging increases GC proliferation and inhibits apoptosis [131], HIF-1 produces the angiogenic miR-382, which targets *TPTH* [132], miR-382 suppresses ovarian cancer migration and invasion by targeting *ROR1* and controlling *EMT* [133]. *PLCG2* downregulation in vitro reduced cellular survival, and proliferation [134], overexpression brought on by hyperinsulinemia is likely to have increased cell proliferation. These novel results might expand our understanding of the WWC2-AS2/-miR-382/*PLCG2* ceRNA regulation network in PCOS development. This sheds information on ceRNA's diagnostic and therapeutic potential for PCOS.

3.2.3. *H19/miR-19b/CTGF*

Sun et al. (2020) investigated the regulatory axis involving H19/miR-19b/CTGF and its implications in PCOS. The study revealed that H19 competes with miR-19b to regulate *CTGF* expression, with H19 positively regulating *CTGF* and negatively regulating miR-19b. The overexpression of *CTGF*, mediated by H19, was found to influence granulosa cell proliferation, apoptosis, and contribute to PCOS through interactions within the ceRNET [135]. Additionally, the study highlighted the involvement of H19 and *STAT3* in regulating ovarian tissue and granulosa cell development in PCOS [136], H19 overexpression was shown to disrupt ovarian *CYP17* and testosterone production in GCs [137]. On the other hand, miR-19b was found to target *IGF-1*, thereby suppressing ovarian granulosa cell growth in PCOS [138]. Interestingly,

miR-19b has also been observed to be overexpressed in normal plasma cells [139]. Regarding *CTGF*, it plays a crucial role during follicular development and corpus luteum formation following ovulation [140]. *CTGF* mRNA expression was significantly observed in preantral and early antral follicles, and its levels increase in porcine GCs during early antral follicle development [140,141]. These findings highlight the diagnostic and therapeutic potential of ceRNETs in PCOS and provide valuable insights into the H19/miR-19b/CTGF regulatory axis.

3.2.4. HCP5/miR-27a-3p/IGF-1

The results of a recent study conducted by Chen et al., in 2020 confirmed the existence of a new ceRNETs involving HCP5/miR-27a-3p/*IGF-1*. In this network, Lnc-HCP5 positively regulates *IGF-1* while negatively inhibiting miR-27a-3p. The down-regulation of HCP5 leads to a decrease in *IGF-1* levels, resulting in the suppression of cell proliferation and an increase in apoptosis in KGN cells. Conversely, miR-27a-3p directly binds to the 3′ UTR of *IGF-1* and promotes cell proliferation [142]. MiR-27a-3p has been identified as an oncogene in various cancers, including gastric cancer [143], osteosarcoma [144], and BRCA [145]. It is also found to be overexpressed in PCOS patients [146] and mice GCs [147]. Another study has shown that miR-323-3p targets *IGF-1*, thereby controlling steroidogenesis and cell death in PCOS [148]. Moreover, increased *IGF-1* levels have been implicated in the pathophysiology of PCOS, contributing to elevated androgen levels [149]. Additionally, PCOS patients with early miscarriage have been found to exhibit increased *IGF-1* and reduced *IGFBP-1* levels [150]. These findings not only underscore the diagnostic and therapeutic potential of ceRNETs in PCOS but also enhance our understanding of the HCP5/miR-27a-3p/*IGF-1* ceRNA regulatory network in PCOS.

3.2.5. MALAT1/miR-125b/TGFβR1

In 2020, Zhang et al. conducted a study that confirmed the presence of the MALAT1/miR-125b/*TGFβ* ceRNA axis. In this axis, the long non-coding RNA MALAT1 positively regulates *TGFβR1* by competing with miR-125b. This interaction leads to the inhibition of granulosa cell (GC) proliferation, and subsequently, *TGFβ* promotes GC dysfunction in PCOS [151]. MALAT1 has been shown to bind with *PARP1* and DNA ligase III, thereby promoting DNA repair signaling in myeloma cells [152]. It also plays a role in modulating gene expression [153], and alternative splicing [154]. Downregulation of MALAT1 has been found to inhibit P53 degradation by binding to MDM2 [155]. MALAT1 expression has been associated with pregnancy loss [156], endometriosis [157], and the promotion of ovarian cancer [158] and HCC [159]. On the other hand, miR-125b has been shown to promote BRCA [160] and leukemia [161], but acts as a tumor suppressor in gastric cancer [162] and HCC [163]. These findings underscore the potential of ceRNETs in the diagnosis and treatment of PCOS and contribute to our understanding of the regulatory network involving MALAT1/miR-125b/*TGFβR1* in the etiology of PCOS.

3.2.6. MALAT1/miR-203a/TGβR2

Concurrently, Zhang et al. study results MALAT1/miR-203a/*TGβR2* has a significant ceRNET in PCOS. The utility of miR-203a-3p as a valuable diagnostic and prognostic biomarker for the spectrum of thyroid neoplasia [164]. Extensive research has confirmed the significant role of miR-203 and its diverse mature miRNAs, including miR-203a and miR-203b, as tumor suppressors in the pathogenesis and advancement of human malignancies [165,166]. Prior studies have indicated that *TGFβR2* plays a pivotal role in the development and progression of ovarian cancer [167,168]. Besides, the upregulation of *TGFβR2* has been observed to enhance cellular proliferation and angiogenesis in various tumor types [169]. The current results document highlights the potential of ceRNETs in the diagnosis and treatment of and enhance our comprehension of the regulatory network encompassing MALAT1/miR-203a/TGFβR2 in the development of PCOS.

3.2.7. ZFAS1/miR-129/HMGB1

In 2020, Zhu et al. uncovered the competitive endogenous RNA network involving ZFAS1/miR-129/*HMGB1* in PCOS GCs. They found that the lnc-RNA zinc finger antisense 1 (ZFAS1) act as a sponge for miR-129 and positively regulates high-mobility group box protein 1 (*HMGB1*). Overexpression of ZFAS1 and *HMGB1* leads to increased apoptosis and decreased cell proliferation in PCOS GCs, while the opposite effect is observed when their expression is reduced [170]. Additionally, ZFAS1 has been implicated in regulating p53-dependent cell cycle and apoptosis in CRC by interacting with *CDK1* [171], as well as promoting clear cell renal cell carcinoma growth and metastasis by targeting miR-10a/*SKA1* [172]. Furthermore, MALAT1 controls the miR-129-5p/*HMGB1* axis to promote colon cancer growth [173], and miR-129 targets *ABCB1* to influence ovarian cancer paclitaxel resistance [174]. It has been demonstrated that upregulation of *HMGB1* contributes to PCOS in adolescents [175]. Collectively, these findings shed light on the role of the ZFAS1/miR-129/*HMGB1* ceRNA regulatory network in PCOS development and provide insights into its diagnostic and therapeutic potential.

3.2.8. HOTAIRM1/miR-433-5p/PIK3CD

The HOTAIRM1/miR-433-5p/*PIK3CD* axis is proposed as a ceRNET according to current research. In PCOS tissues, HOTAIRM1 positively up-regulate *PIK3CD* with sponging mR-433-5p, while negatively modulate miR-433-5p. Functional experiments have proven that overexpression of HOTAIRM1 inhibits granulosa cell proliferation and promotes apoptosis, whereas overexpression of miR-433-5p enhances cell production and reduces apoptotic ability by targeting *PIK3CD* [176]. It is worth noting that HOTAIRM1 downregulation has been identified as a potential biomarker in CRC [177] and may serve as a therapeutic target in tamoxifen-resistant estrogen-positive BRCA patients [178]. Additionally, HOTAIRM1 suppresses stomach cancer through its interaction with miR-17-5p, which controls *PTEN* expression [179]. MiR-433-5p has been implicated in the regulation of multiple pathways [53]. Studies have shown that overexpression of miR-433-5p prevents motor impairment and inflammation by targeting *MAPK1* [180]. Moreover, miR-433-5p has been reported to suppress cancer cell proliferation and metastasis by modulating tumor signaling pathways or target genes [181]. Lower levels of hepatic *PIK3CD* in type 2 diabetes have been associated with decreased insulin sensitivity induced by miR-125b [182]. In light of the current research, the HOTAIRM1/miR-433-5p/-*PIK3CD* axis emerges as a potential target for prognostic and therapeutic interventions in PCOS. Further investigation into the regulatory mechanisms and functional implications of this ceRNET could provide valuable insights for PCOS management.

3.2.9. BC036229/miR-628-5p/HSD17B7

The BC036229/miR-628-5p/HSD17B7 axis was reported by Zhao et al. as ceRNETs involved in 2021 [183], present an interesting ceRNA regulatory mechanism. BC036229 is proposed to inhibit miR-628-5p, which in turn regulates the expression of *HSD17B7* gene. These findings suggest the ceRNA axis play a role in the control of steroid production and metabolic pathways during PCOS development. Furthermore, the BC036229/miR-628-5p/*HSD17B7* axis is implicated in the biosynthesis and metabolic processes related to steroid hormones [62]. Notably, miR-628-5p has been proven to target *FGFR2*, thereby reducing tumorigenicity in OC [184]. In HCC, the miR-628-5p/*MEIS2* axis promotes cell motility, invasion, and epithelial to mesenchymal transition (EMT) through the activation of Notch signaling [185]. Additionally, in glioblastoma, circ_0001801 controls cell growth, migration, invasion, and EMT by modulating the miR-628-5p/*HMGB3* axis [186]. Taken together, these ceRNA axes modulate steroid synthesis and amino acid metabolism pathways, suggesting their involvement in the regulation of PCOS. The identification of these ceRNETs holds potential as diagnostic and therapeutic biomarkers for PCOS management.

3.2.10. AY603498/miR-628-5p/CYP11A1

Concurrently Zhao et al. was reported AY603498/miR-628-5p/*CYP11A1* as ceRNET in PCOS etiology [183]. Although this study only reported a role of this ceRNET through the RNA-sequencing experiment it should be further analysis the exact role of lncRNA-miRNA-mRNA in ongoing functional studies. However, lncRNA-miR-628-5p/*CYP11A1* regulatory axis exhibits an association with both steroid hormone biosynthesis and metabolic pathways. The role of miR-628-5p well established in multiple reproductive cancers instance, the miR-628-5p inhibits the growth of epithelial ovarian cancer cells by targeting *FGFR2* [184], in the context of cervical carcinoma, miR-628-5p has been identified as a tumor suppressor that exerts its effects by targeting *VEGF*. Specifically, miR-628-5p promotes apoptosis of carcinoma cells and inhibits cell proliferation [187], Martinez et al., study proven differential expression analysis in women who developed severe preeclampsia exhibited elevated levels of miR-628-5p in their serum at 20 weeks of gestation. The present investigation observed a downregulation of the miR-628-5p-/*CYP11A1* network in granulosa cells (GCs) affected by polycystic ovary syndrome (PCOS) [188]. Furthermore, the *CYP11A1* is key gene implicated in the biosynthesis and metabolic processes related to steroid hormones [62].

3.2.11. AK097578/miR-548i/IDH1

The AK097578/miR-548i/*IDH1* was reported as another ceRNET in PCOS, lncRNA-AK097578 with sponging miR-548i targets *IDH1* and positively regulate *IDH1* which may implications for amino acid metabolism and mitochondria-cytoplasm transfer [183]. A member of the miR-548 family, miR-548i was first identified in the GCs of human pre-ovulatory follicles. The intronic region of the follicle-stimulating hormone receptor (*FSHR*) gene contains the miR-548 gene [189]. A previous study demonstrated that *IDH1* plays a crucial role in safeguarding murine hepatocytes against oxidative stress through its regulation of the intracellular NADP+/NADPH ratio [190]. The downregulation of *IDH1* expression resulted in an imbalance in *NADPH* levels, leading to the occurrence of oxidative stress damage or heightened susceptibility of cells to oxidative stress [191]. Furthermore, the down-regulation of *IDH1* resulted in the accumulation of reactive oxygen species (ROS) and the disturbance of the redox balance, consequently impacting cell proliferation and survival [192]. Moreover, recent research has demonstrated a correlation between *IDH1* and follicular atresia as well as ovarian aging [27,28].

3.2.12. AK128202/miR-483-5p/GOT2

On the other hand, targeting GOT2 can modulate amino acid metabolism and NADPH production. MiR-548i has been implicated in the regulation of HCC [193], and lung cancer (LC) [194]. Previous research has shown lower expression of miR-483-5p in cumulus cells of PCOS patients [195]. It has been found that miR-483-5p can regulate the expression of Notch3/MAPK3 and other miRNA profiles [196]. Additionally, the acetylation of GOT2 has been associated with mitochondrial metabolism [197]. Based on these findings, it is reasonable to hypothesize that miR-483-5p may regulate GOT2 and contribute to insulin resistance in PCOS. Women with PCOS exhibit various transcriptional and epigenetic alterations in GCs, which are linked to steroid hormone production and metabolic pathways. The involvement of lncRNAs/miR-628-5p-CYP11A1, HSD17B7, and lncRNAs/miR-483-5p-GOT2 in PCOS pathogenesis highlights their potential as biomarkers or therapeutic targets.

3.2.13. LINC00173/miR-124-3p/JAG1

Recent studies have supported the ceRNA theory, which involves the competitive interaction of RNA molecules. Chen et al. investigated the role of the LINC00173/miR-124-3p/JAG1 axis and its potential significance in PCOS [198]. Their findings demonstrated that LINC00173 negatively influences miR-124-3p while positively regulating JAG1. Moreover, LINC00173 was shown to promote apoptosis and growth. In PCOS, the abundance of miR-124-3p was found to be inversely correlated with LINC00173 and JAG1 levels [198]. While studies in other diseases have implicated LINC00173 in the regulation of Etk expression through miR-218 sponging [199], as well as the regulation of miR-490-3p to promote triple-negative BRCA development [200], and NUTF2 expression through miR-765 sponging to promote glioma tumorigenesis [201]. In addition to its role in PCOS, miR-124-3p has been implicated in other diseases. For instance, in nephrolithiasis, miR-124-3p has been shown to accelerate cell death and enhance cell proliferation [202]. Moreover, miR-124-3p has demonstrated the ability to reduce apoptosis induced by lipopolysaccharide (LPS) in macrophage cells [203]. These studies highlight the multifaceted nature of miR-124-3p and its involvement in various cellular processes. Although the functional outcomes of LINC00173/miR-124-3p/JAG1 interactions in PCOS are yet to be fully elucidated, these findings support the ceRNA theory and suggest that LINC00173 may serve as a potential biomarker in the diagnosis and treatment of PCOS. Further studies specifically focused on PCOS are warranted to validate the involvement of this ceRNET (Table 2 & Fig. 3).

3.3. LncRNA, miRNA, mRNA ceRNETs in rodent models

3.3.1. HOTAIR/miR-130a/IGF1

In 2019, Jiang et al. validated an important ceRNET involving HOTAIR/miR-130a/IGF1. HOTAIR functions through a sponge-like mechanism, competing with miR-130a for binding to the target IGF1. HOTAIR negatively regulates miR-130a while positively regulating IGF1 in PCOS cells [204]. The miR-130a/TGF-1 axis, through its modulation of granulosa cell apoptosis, plays a crucial role in fertility [205]. Furthermore, miR-130a, by targeting TSC1, promotes the progression of severe-grade ovarian cancer [206]. Overexpression of IGF1 leads to decreased proliferation and increased apoptosis in ovarian GCs [147]. In PCOS, steroidogenesis is regulated by IGF-1 through the miR-323-3p/IGF-1 pathway [148]. Notably, IGF-1 may play an important role in the pathophysiology of PCOS in rats, contributing to increased androgen production [149]. According to current understanding, HOTAIR acts as a sponge for miR-130a, exerting control over ovarian granulosa cell proliferation through ceRNA regulation. These findings shed light on the HOTAIR/miR-130a/IGF1 axis in PCOS, highlighting the diagnostic and therapeutic potential of ceRNETs for this condition.

3.3.2. RT1-M3-1-002/miR-146a-5p/Csmd1

The ceRNET involving RT1-M3-1-002/miR-146a-5p/Csmd1 was discovered and characterized by Fu et al., in 2018. The hypothesis suggests that RT1-M3-1-002, when acting as a sponge for miR-146a-5p, could modulate the function of miR-146a-5p and bind to Csmd1. The long non-coding RNA (lncRNA) RT1-M3-1-002 negatively influences miR-146a-5p while exerting a positive effect on Csmd1. Additionally, the levels of RT1-M3-1-002/Csmd1 were found to increase, while miR-146a-5p levels decreased in a PCOS rat model [207]. Aberrant expression of Csmd1 has been associated with autoimmune diseases, insulin resistance, and steroid hormone pathways. MiR-146a-5p, which is closely related to PCOS [208], has been implicated as a tumor suppressor in BRCA [209] and downregulated in GCs [210]. These findings contribute to a better understanding of the RT1-M3-1-002/miR-146a-5p/Csmd1 axis in PCOS. They demonstrate the diagnostic and therapeutic potential of ceRNETs in the treatment of PCOS and shed light on the regulatory mechanisms involving the RT1-M3-1-002/miR-146a-5p/Csmd1 network.

3.3.3. CD36-005/miR-448-5p/Ltbp4

In line with a previous study, the CD36-005/miR-448-5p/Ltbp4 axis in PCOS rats demonstrates agreement with prior research findings. CD36-005 acts as a sponge for miR-448-5p, leading to its adverse modulation. Conversely, CD36-005 positively regulates Ltbp4. The

Table 2
LncRNAs, miRNAs, mRNAs ceRNAs in PCOS.

Organism	CeRNETs	Regulator	Inhibited		Targeted		Remarkable pathogenicity		Functional	Treated cells	Refs
Human	lncRNA, miRNA, mRNA	PWRN2	P ↑ N ↓	miR-92b-3p	P ↓ N ↑	*TMEM120B*	P ↑ N ↓	↑ Ad, ↑ SO ↓ Ad, ↓ SO	Dual-luciferase reporter assay	GCs, KGN	[122]
		WWC2-AS2	P ↑ N ↓	miR-382	P ↓ N ↑	*PLCG2*	P ↑ N ↓	↓ CP, ↑ Ap ↑ CP, ↓ Ap	–	GCs	[127]
		H19	P ↑ N ↓	miR-19b	P ↓ N ↑	*CTGF*	P ↑ N ↓	↓ CP, ↑ Ap ↑ CP, ↓ Ap	Dual-luciferase reporter assay	GCs, KGN	[135]
		HCP5	P ↓ N ↑	miR-27a-3p	P ↑ N ↓	*IGF-1*	P ↓ N ↑	↓ CP, ↑ Ap ↑ CP, ↓ Ap	Dual-luciferase reporter assay	KGN	[142]
		MALAT1	P ↓ N ↑	miR-125b	P ↑ N ↓	*TGFβR1*	P ↓ N ↑	↑ CP, ↓ Ap ↓ CP, ↑ Ap	Dual-luciferase reporter assay	GCs	[151]
			P ↓ N ↑	miR-203a	P ↑ N ↓	*TGβR2*	P ↓ N ↑	↑ CP, ↓ Ap ↓ CP, ↑ Ap			
		ZFAS1	P ↑ N ↓	miR-129	P ↓ N ↑	*HMGB1*	P ↑ N ↓	↓ CP, ↑ Ap ↑ CP, ↓ Ap	Dual-luciferase reporter assay	GCs	[170]
		HOTAIRM1	P ↑ N ↓	miR-433-5p	P ↓ N ↑	*PIK3CD*	P ↑ N ↓	↓ CP, ↑ Ap ↑ CP, ↓ Ap	Dual-luciferase reporter assay	GCs, KGN	[176]
		BC036229	P ↑ N ↓	miR-628-5p	P ↓ N ↑	*HSD17B7*	P ↑ N ↓	↓ SHB ↑ SHB	–	GCs	[183]
		AY603498	P ↑ N ↓	miR-628-5p	P ↓ N ↑	*CYP11A1*	P ↑ N ↓	↓ SHB ↑ SHB			
		AK097578	P ↑	miR-548i	P ↓	*IDH1*	P ↑	↓ AAM, NAD-m			
			N ↓		N ↑		N ↓	↑ AAM, NAD-m			
		AK128202	P ↑	miR-483-5p	P ↓	*GOT2*	P ↑	↓ AAM, NAD-m			
			N ↓		N ↑		N ↓	↑ AAM, NAD-m			
		LINC00173	P ↑ N ↓	miR-124-3p	P ↓ N ↑	*JAG1*	P ↑ N ↓	↓ CP, ↑ Ap ↑ CP, ↓ Ap	Dual-luciferase reporter assay	GCs, KGN, Rats.	[198]

Apoptosis (Ap), Adipogenesis (Ad), Amino acid metabolism (AAM), Cell proliferation (CP), Competitive endogenous RNA Networks (CeRNETs), Granulosa cell (GC), Human granulosa-like tumor cell line (KGN), NAD(H) metabolism (NAD-m), Normal (N), Patients (P), Severe Obesity (SO), Steroid hormone biosynthesis (SHB).

expression of CD36-005 and Ltbp4 was found to be elevated in PCOS model rats, while miR-448-5p exhibited a reduction in PCOS [207]. Ltbp4 is involved in various cellular processes such as apoptosis, RAC1, and mitochondrial pathways. It plays a role in controlling the activation of TGF-beta by maintaining its latent form during extracellular storage and may hold therapeutic potential in conditions like renal fibrosis and disease protection [211]. Aberrant expression of Ltbp4 has been associated with Duchenne muscular dystrophy (DMD) [212]. MiR-448-5p, which is closely related to PCOS [208], acts as a tumor suppressor in BRCA [209] and is downregulated in GCs [210]. The findings from our study contribute to a better understanding of the CD36-005/miR-448-5p/Ltbp4 axis in PCOS. This highlights the diagnostic and therapeutic potential offered by ceRNETs for PCOS. Please refer to Table 3 and Fig. 4.

4. Remarkable conclusions

PCOS is a complex condition characterized by a cascade of biological events resulting from molecular interactions among gene products. Despite advancements in understanding the genetic mechanisms underlying PCOS, it remains a significant cause of female infertility, indicating that the underlying operations are more intricate than previously believed. In recent years, the concept of competitive endogenous RNA networks (ceRNETs) has emerged as a crucial area of research, exploring the interplay among different RNA classes within the vast RNA universe. Within PCOS research, ceRNETs represent a novel and promising avenue that can greatly enhance our understanding of the molecular processes driving polycystic ovarian syndrome and its pathophysiology. In this study, we conducted a comprehensive review of validated ceRNAs, including non-coding RNAs such as lncRNAs, miRNAs, and mRNAs [122,127,135,142,151,170,176,183,198] Additionally, we reviewed ceRNAs composed of circRNAs, miRNAs, and mRNAs [47,48,49,50,51,52,53]. Furthermore, we emphasized on role of ceRNAs associated with PCOS in rodent as animal models, encompassing lncRNAs, miRNAs, and mRNAs [204,207]. However, it should be noted that only a subset of these ceRNAs has been validated thus far. This limitation arises from the fact that research on PCOS-related ceRNAs is still in its nascent stages. However, there are still several ceRNAs that require functional investigation for validation. While researchers have extensively focused on mRNA and miRNAs, there remain numerous unanswered questions regarding the involvement of long non-coding RNAs (lncRNAs), circRNAs, and transcribed pseudogenes in PCOS development. The role of these non-coding RNAs, as well as the potential involvement of transcript pseudogenes, have not been fully explored in the context of PCOS. Recently, circRNAs have garnered significant attention as they emerge as important players in ceRNETs. It is crucial for researchers to direct their efforts towards identifying additional ceRNAs within these categories to ascertain the extent to which ceRNA crosstalk represents a widespread network of RNA regulation. The discovery of new classes of ceRNAs opens up exciting avenues for future research. Notably, Argonaute proteins have been reported to bind with transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs), suggesting that these commonly occurring stable, small RNA species may also function as ceRNAs [213]. Additionally, intriguingly, 3′ untranslated regions (UTRs) have been identified as independently induced entities, separate from their associated protein-coding regions, in humans, mice, and flies. This observation implies that 3′ UTRs may represent a novel class of ceRNAs [214]. These findings provide further evidence of the complexity and diversity of ceRNA-mediated regulatory networks, warranting continued exploration in PCOS research and beyond.

Ethics approval and consent to participate

Not applicable.

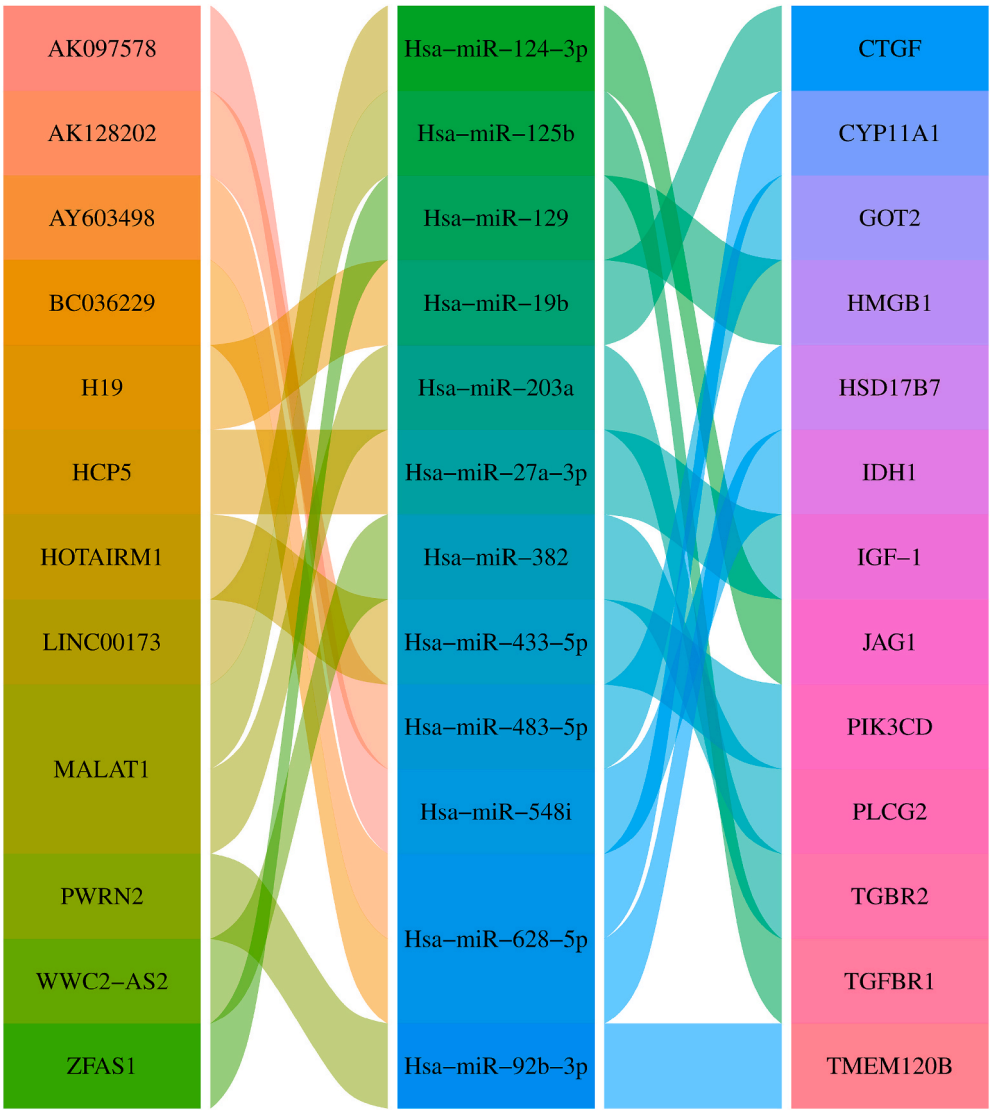

Fig. 3. The alluvial plot ceRNA construction of competitive endogenous RNA networks in women with PCOS. The left column represents lncRNAs, the center column represents miRNAs, and the right column represents mRNAs. Stream blocks between the columns represent correlation between axes.

Table 3
CeRNETs, lncRNAs, miRNAs, mRNAs in PCOS rodent models.

Organism	CeRNETs constructure	Regulator		Inhibited		Targeted		Remarkable pathogenicity	Functional validation	Treated cells	Refs
Rodent	lncRNAs, miRNA, mRNA	HOTAIR	P ↑ N ↓	miR-130a	P ↓ N ↑	IGF1	P ↑ N ↓	↓ CP, ↑ Ap ↑ CP, ↓ Ap	Dual-luciferase reporter assay	Rat, GCs	[204]
		RT1-M3-1-002	P ↑ N ↓	miR-146a-5p	P ↓ N ↑	Csmd1	P ↑ N ↓	↑ IR ↓ IR	Q-RT-PCR	Rat	[207]
		CD36-005	P ↑ N ↓	miR-448-5p	P ↓ N ↑	Ltbp4	P ↑ N ↓	↑ IR ↓ IR			

Apoptosis (Ap), Competitive endogenous RNA Networks (CeRNETs), Granulosa cell (GC), Inflammatory Reactions (IR), Normal (N), Patients (P).

Consent for publication

We affirm that all listed co-authors have reviewed and approved the final version of the article and consent to its publication.

Availability of data and materials

The data used to support the findings of this study are included in the article.

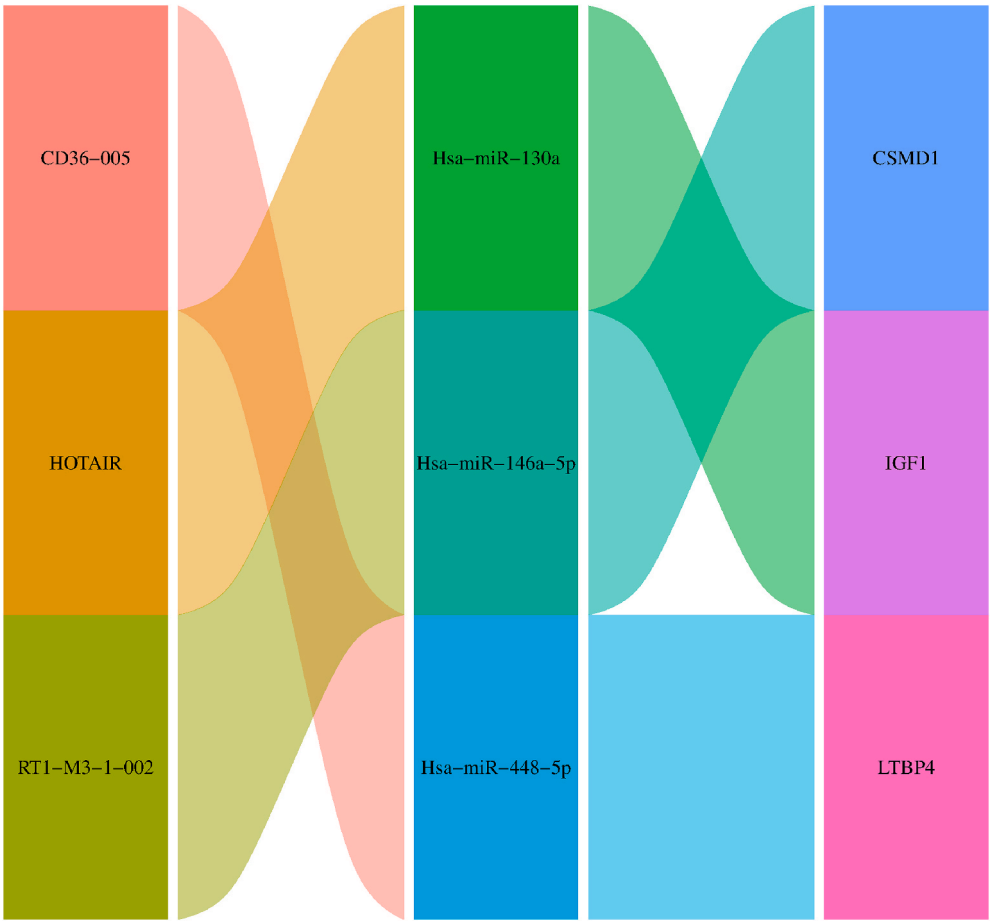

Fig. 4. The alluvial plot ceRNA construction of competitive endogenous RNA networks in rodent PCOS animal model. The left column represents lncRNAs, the center column represents miRNAs, and the right column represents mRNAs. Stream blocks between the columns represent correlation between axes.

Funding

Not applicable.

Declaration of competing interests

The authors declare no potential conflicts of interest.

CRediT authorship contribution statement

Roozbeh Heidarzadehpilehrood: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Maryam Pirhoushiaran:** Writing – review & editing, Writing – original draft, Supervision, Software, Project administration, Investigation, Data curation.

Acknowledgement

Not applicable.

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