International Electronic Journal of Medicine

Int Electron J Med. 2020; 9(2):86-91

doi 10.34172/iejm.2020.15

Mini Review

Manifestly Altered MicroRNAs in Poly Cystic Ovary Syndrome

Mahta Moraghebi[1], Milad Rafat[1], Pegah Mousavi[2], Kianoosh Malekzadeh[2*]

[1]Student Research Committee, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
[2]Department of Medical Genetics, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

Abstract
MicroRNAs (miRNAs) constitute a large family of small non-coding RNAs which regulate gene expression at the surface following transcription. They are widely involved in many physiological and pathological processes including polycystic ovarian syndrome (PCOS). PCOS is an endocrine disorder in women. Currently, there is no comprehensive information about the role of miRNAs in PCOS. Thus, this paper has attempted to collate studies on miRNAs in order to determine important changes in their miRNA expression profile in the total blood, serum, plasma, follicular fluid, and granulosa cells in PCOS patients alongside the genes which are targeted for regulation by these miRNAs. This study presents a new approach for using miRNAs and their target genes for diagnosing and treating PCOS.
Keywords: MicroRNA, Small non-coding RNA, Polycystic ovary cancer

Received: January 1, 2020, Accepted: June 2, 2020, ePublished: June 30, 2020

***Correspondence to**
Kianoosh Malekzadeh, Department of Medical Genetics, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
Mobile: (+98)9176108396
Email: keyanoosh@gmail.com

Introduction

Polycystic ovarian syndrome (PCOS) is a common heterogeneous endocrine disorder in women during reproductive ages. Principally, there are three diagnostic criteria proposed by different groups including the National Institute of Health/National Institute of Children's Health and Disease (1), the European Society of Human Reproduction and Embryology/the American Society of Reproductive Medicine (2), and the Excessive Androgen Association and PCOS (3). The prevalence of PCOS ranges from 6 to 20% given the type of the applied criteria (4-6). According to all available criteria, the diagnosis of PCOS is usually based on dysmenorrhea, hyperandrogenism, and polycystic ovary detected by sonography. The typical symptoms of PCOS include oligomenorrhea, amenorrhea, hirsutism, acne, overweight or diabetes, and infertility. Currently, the exact cause of PCOS is unknown. Epidemiological studies suggested that the PCOS profile risk relies on familial history, overweight and obesity (7-9), and diabetes (10).

Post-transcription regulation by microRNAs (miRNAs) has been important research over the past 10 years. miRNAs constitute a large family of small non-coding RNAs with a length of 19-25 nucleotides (11,12). The production and function of miRNAs are shown in Figure 1. miRNA genes are usually transcribed by the RNA polymerase II/III and bound to pri-miRNA. They are then processed by Drosha in order to convert to pre-microRNAs. Next, they migrate to the cytoplasm and are changed into mature miRNAs by the Dicer. In addition, miRNAs attach to the 3' UTR region of target genes causing the total or partial inhibition of gene transcription (13). The total inhibition of miRNA relies on the extent that miRNA complements mRNA and is rarely observed in animals. Thus, the effect of miRNA on mRNA transcription mostly occurs through suppressing and reducing transcription (14). The regulatory mechanisms of miRNAs have been extensively studied in the development of diseases, especially cancers. However, the possible regulatory patterns of miRNAs in PCOS have been poorly examined and require further studies.

Different studies have reported contradictory results on miRNAs in various samples of blood, plasma, serum, ovaries, and to the same extent, in different ovarian components including follicular fluid, granulosa cells, blastocyte, and oocyte (15-18).

Investigating the miRNAs Affecting Hormonal Pathways

miRNAs have a more stable expression in the serum that makes them suitable noninvasive biomarkers for diagnosis and prognosis. Hence, various studies selected

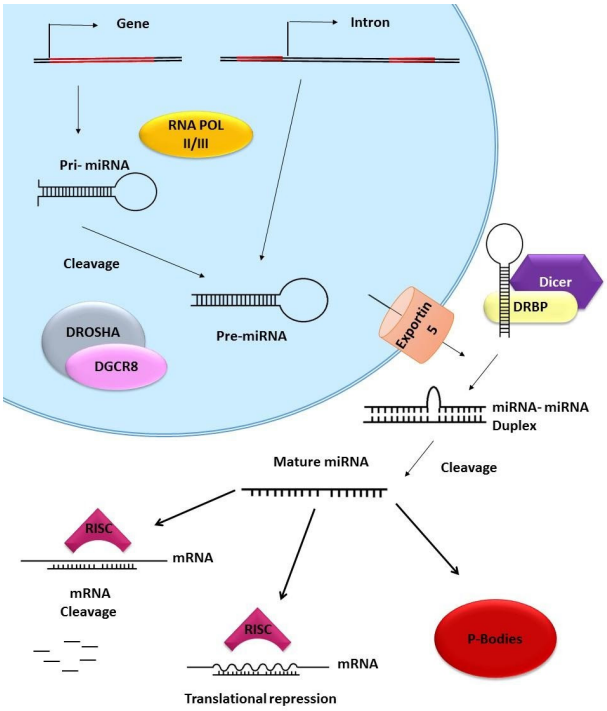

Figure 1. microRNAs Biogenesis.

blood samples as the source of the miRNAs profile. For example, a case-control study indicated that miR-21, miR-27b, miR-103, and miR-155 diminished in the total blood. Further, bioinformatic analyses proposed that these miRNAs can be involved in the metabolism of hormones, especially testosterone (19). In another study, the expression of miRNAs in PCOS patients was compared against control through microarray ad qPCR methods, and the findings revealed that miR-30c, miR-146a, and miR-222 increased significantly in PCOS patients. Relevant analyses indicated that miR-146a was negatively associated with the serum testosterone level. This study also showed that the differentiated miRNAs expressed in ovarian tissues did not match different types in the blood (15, 16, 20). The androgen synthesis in the ovary usually increases in PCOS patients. The ovarian cycle is also impaired due to the abnormal secretion of the hypothalamus-pituitary-ovary axis hormone. In addition, insulin inhibits the hepatic synthesis of sexual hormone-binding globulin, resulting in elevated free testosterone concentration, which leads to the emergence of PCOS symptoms. Some studies examined the relationship between miRNAs and the level of sexual hormone (21, 22). They also showed that miRNAs are involved in the homeostatic modification of steroid hormones, as well as target steroid receptors or steroid synthesis enzymes. miR-222, which was largely expressed in the follicular liquid and serum of PCOS patients (23), is an estrogen receptor regulator 1 (24). It was further reported that miR-320 targets the steroidogenic factor 1 (SF-1) gene although the expression of this miRNA was discrepant across different studies (17).

Investigating the MicroRNAs Affecting Insulin Pathways

In their study, Ding et al found that miRNA is heavily involved in intrinsic immunity, apoptosis, angiogenesis, oxidative stress, as well as the signaling pathway of P53 and mitogen-activated protein kinase/AKT (25).

Subsequent tests indicated that miR-6767-5p was negatively correlated with fasting blood sugar and directly related to the severity of dysmenorrhea (26). Furthermore, PCOS is usually associated with the severe incidence of insulin resistance. In type I diabetes, it was found that the patients with PCOS had an increased risk of developing the disease by around 15.4% as compared to the control group (27). A previous study also showed that the prevalence of PCOS in types I and II diabetes was 24% and 8.3%, respectively (18). In a study by Amini et al (28), these numbers differed from 4.5%-13.4% to 26.7% in a study by Peppard et al (29). Based on the findings of another study, dysregulation in miRNAs can be a target for the key molecules of the insulin signaling pathway (24). Moreover, the role of insulin in the synthesis of androgens can indicate the relationship between these two diseases as the cause and effect (30). Glucose transporter protein type-4 (GLUT-4) is a major insulin-dependent glucose transporter (31) and miR-93 can target GLUT-4. According to previous evidence, the mRNA level of GLUT-4 diminishes by the elevation of miR-93 (30, 32). Additionally, insulin receptor substrates 1 and 2 (IRS1 and IRS2) are considered as cytoplasmic signaling molecules that mediate insulin effects (33). Finally, another previous study reported that IRS2 significantly suppressed through the overexpression of miR-135a, miR-18b, and miR-9 (34).

Conclusion

In general, a close association was observed between the PCOS and many diseases including diabetes, complicating its treatment. Previous studies on miRNAs mostly addressed tissue or cell culture while recent studies have mainly focused on serum samples because the serum miRNA profile may have the potential for providing a good noninvasive biomarker for the diagnosis and prognosis of PCOS or the possibility of the incidence of its associated diseases.

It seemed that changes in the miRNAs involved in steroid and insulin signaling pathways may have a significant relationship with the pathogenesis of PCOS and its associated diseases, which can be candidates for future studies. In addition, the study of miRNAs may set the ground for the emergence of new pharmacologic targets in PCOS and its related diseases.

Although miRNAs and their target genes have been

Table 1. The Studied microRNAs in PCOS

microRNA	Regulations	Species	Tissue/Cell	Major Findings	Reference
miR-9	Up	Human	Follicular fluid; granulosa cells	Inhibits testosterone release; Increases expression of PCNA; Targets IL-8, SYT1, and IRS2	(20, 34, 35)
miR-16	Down	Human	Whole blood	Promotes ovarian granulosa cell proliferation; Suppresses apoptosis through targeting PDCD4	(36)
miR-18b	Up	Human	Follicular fluid; granulosa cells	Promotes progesterone release; Inhibits testosterone and estradiol release; Suppresses PCNA expression; Promotes Bax expression; Targets IL-8, SYT1, and IRS2	(20, 34, 35)
miR-19b	Down	Human:Cell lines	Blastocysts; KGN cells	targeting IGF-1	(37)
miR-21	Up	Human Mouse	Whole blood; serum; follicular fluid; granulosa cells	Blocks apoptosis in mouse periovulatory granulose cells; Decreased in obese individuals or type 2 diabetic patients; Increased to FSH exposure; Targets LATS1	(19, 20, 38-40)
miR-27b	Up	Human	Whole blood	Decreased in obese individuals; Positively correlated with testosterone	(19)
miR-29a-3p	Down	Human	Serum	N/A	(25)
miR-29c-3p	Up	Human	Follicular fluid	N/A	(41)
miR-30c	Up	Human RAT	Serum Granulosa cells	Increased to FSH exposure	(15)
miR-93	Down	Human	Blastocysts	Targets SIRT1 and GLUT4	(32, 37)
miR-99a-3p	Up	Human	Follicular fluid	N/A	(41)
miR-103	Up	Human	Whole blood; granulosa cells	Promotes progesterone release; Inhibit estradiol release; Reduced in obese individuals	(19, 20)
miR-105-3p	Down	Human	Follicular fluid	N/A	(41)
miR-122	Up	Human	Serum	Increased in PCOS patients with impaired glucose metabolism	(41)
miR-124-3p	Down	Human	Serum	N/A	(25)
miR-125a-5p	Up	Human	Follicular fluid	N/A	(41)
miR-128	Down	Human	Serum	N/A	(25)
miR-130b-3p	Down	Human	Serum	Increased DENND1A.V2, cytochrome P450 17α-Hydroxylase (CYP17A1) and androgen biosynthesis	(42)
miR-132	Down	Human RAT	Follicular fluid; granulosa cells	Increases estradiol secretion; Inhibits progesterone and testosterone release; Increases PCNA exposure; Increased after hCG-induced ovulation and FSH exposure; Inhibits Bax expression; Targets HMGA2 and Ctbp1	(16, 20, 43)
miR-135a	Up	Human	Follicular fluid; granulosa cells	Reduces progesterone and testosterone release; Inhibits Bax expression; Targets IL-8, SYT1, and IRS2	(34, 35)
miR-146a	Up	Human	Serum; follicular fluid; granulosa cells	Suppresses release of progesterone, estradiol, and testosterone	(15, 16, 20)
miR-155	Up	Human	Serum; follicular fluid; granulosa cells	Inhibits testosterone release; Decreases PCNA expression; Inhibits Bax expression	(19,20)
miR-193b	Up	Human	Serum	Increased in PCOS patients with impaired glucose metabolism than in PCOS patients with normal glucose tolerance	(15)
miR-194	Up	Human	Serum	Increased in PCOS patients with impaired glucose metabolism than in PCOS patients with normal glucose tolerance	(15)
miR-199b	Down	Human	Serum	N/A	(15)
miR-200a	Up	Human	Follicular fluid	N/A	(41)
miR-200b	Up	Human	Follicular fluid	N/A	(41)
miR-222	Down/UP	Human: RAT	Ovary; granulosa cells	Increased in type 2 diabetes patients; Increases estradiol release; Targets estrogen receptor 1; P27 and KIP1	(15, 16, 23, 24)
miR-224	Up	Human; Mouse	Follicular fluid Cumulus-oocyte Granulosa cells	Promotes granulose cell proliferation; Increases estrogen release; Targets PTX3 and Smad4	(34,44)

miR-320	Up/Down	Human; Mouse	Serum; Follicular fluid; Granulosa cells	Decreased in serum; Up-regulated in follicular fluid and granulose cells; Down-regulated with TGF-β1 treatment; Increased in insulin resistance; Targets RAB5B, E2F1, and SF-1	(15-17)
miR-324	Down	Human	Serum	N/A	(45)
miR-383	Up	Human; Mouse	Follicular fluid; Granulosa cells; Oocytes	Increases estradiol release; Decreased by TGF-β1	(17,34,46)
miR-451a	Down	Human	Serum	N/A	(37)
miR-592	Down	Human	Serum; Granulosa cells	Inhibits cell viability and transition from phase G1 to phase S; Targets LHCGR	(47)
miR-638	Up	Human	Serum	N/A	(25)
miR-652-3p	Down	Human	Serum	N/A	(37)
miR-3665	Up	Human	Serum	N/A	(25)
miR-4463	Up	Human	Serum	N/A	(25)
miR-4522	Down	Human	Serum	N/A	(45)
miR-5706	Up	Human	Serum	N/A	(25)
miR-6767-5p	Down	Human	Serum	Positively correlated with SHBG; Negatively correlated with FAI	(26,45)
let-7c	Down	Human	Serum	N/A	(25)
let-7i-3p	Up	Human	Serum	N/A	(25)

N/A: not available

Note. PCOS: poly cystic ovary syndromes; PCNA: proliferating cell nuclear antigen; IL-8: *interleukin 8*; SYT1: *synaptotagmin* 1; IRS2: insulin receptor substrate 2; PDCD4: programmed cell death 4; IGF-1: *insulin-like growth factor 1*; FSH: *follicle stimulating hormone*; LATS1: large tumor suppressor homolog 1; SIRT1: sirtuin (silent mating type information regulation 2 homolog) 1; GLUT4: glucose transporter protein type-4; hCG: human chorionic gonadotropin; HMGA2: High mobility group protein A2; Ctbp1: C-terminal binding protein 1; PTX3: pentraxin 3; RAB5B: Ras-related protein Rab-5B; TGF-β1: transforming growth factor-β; LHCGR: luteinizing hormone/choriogonadotropin receptor; SHBG: *sex hormone-binding globulin*; FAI: free androgen index; DENND1A: DENN domain containing 1A.

reported (Table 1), it seems that extensive studies are required so that to create a panel of microRNAs which can be used with high sensitivity and specificity in creating the kits to diagnose PCOS and the probability of the incidence of its associated diseases. Accordingly, it provides the chance for determining the prognosis of the PCOS spectrum and the stage of the disease, and eventually, specifying the degree of the success of therapeutic strategies. It is also possible that by knowing the changes in the expression profile of this group of molecules, its pathogenesis mechanisms would become clear and new drugs apart from hormone therapy could emerge for its treatment or control.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

Acknowledgment

This research was partially supported by Hormozgan University of Medical Science. We thank our colleagues from the Student Research Committee for providing insight and expertise that greatly assisted the research although they may not agree with all the conclusions of this paper.

Ethical Statement

Not applicable.

Authors' Contribution

MM wrote the manuscript. MR, PM, and KM collected the data, revised the literature, and contributed to the conception and design of the study. Eventually, all authors contributed to the critical revision, edition, and final approval of the manuscript.

Funding/Support

There is no funding for this article.

Informed Consent

Not applicable.

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