Emerging Role of the ceRNA-Based MALAT-1-miRNA Network in Polycystic Ovary Syndrome

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a hormonal disorder and a common health problem that affects women at the early to late reproductive stage. Several genetic and environmental factors such as obesity, liver diseases, imbalance of androgens, and menstrual dysfunction have contributed to the progression of PCOS. Research has shown a link between diabetes, hypertension, miscarriages, and cardiovascular disease with PCOS. Experimental discoveries have begun to evaluate the mechanisms involved in PCOS. Although various classical interventions are used in the treatment of PCOS, current medications are not able to control outcomes of PCOS and the management of this syndrome is still challenging. Accumulating evidence showed that dysregulation of long non-coding RNAs (lncRNAs) is essential to PCOS pathogenesis. LncRNAs are a class of transcripts that mediate the process of gene expressions at the level of transcription and post-transcription. It has been found that lncRNA metastasis-associated lung adenocarcinoma transcript-1 (MALAT1 or nuclear-enriched abundant transcript 2 (NEAT2)) presents a vital role in regulating PCOS. MALAT-1 as a competing endogenous RNA (ceRNA) can suppress microRNAs (miRNAs) and decrease granulosa cell proliferation, apoptosis, and pathogenesis. Abnormal expression of MALAT1 is one of the prognostic factors for cell autophagy, migration, and drug resistance. MALAT1 can be used as a potential biomarker for treatment of PCOS. However, the exact roles of MALAT1 in granulosa cells of women with PCOS remain largely unknown and further studies are required to confirm its action. In the present article, we summarize the functions of the lncRNA MALAT-1/miRNA axes in women with PCOS.

Keywords: Polycystic ovary syndrome, MALAT-1, LncRNA, Pathogenesis

Introduction

Polycystic ovary syndrome (PCOS) is an important endocrine problem and a heterogeneous disorder that develops in reproductive-aged women **(1, 2)**. This multifactorial disease with a prevalence between 5% to 15% can disrupt ovarian and reproductive function, and cause infertility **(3)**. PCOS symptoms can be divided into a few PCOS-linked, mild, severe, or all PCOS-linked symptoms **(4)**. PCOS is commonly associated with hormonal imbalance or hyperandrogenism **(5)**, dyslipidemia **(6)**, insulin resistance **(7)**, dysglycemia **(8)**, oxidative stress **(9)**, obesity **(10)**, menstrual dysfunction **(11)**, non-alcoholic fatty liver disease **(12, 13)**, and cardiometabolic risk **(14, 15)**. Several environmental **(4)**, genetic **(16, 17)**, and intra-uterine factors **(18)** are thought to be important for the development of PCOS **(19)**. Currently, various pharmacological treatment options **(20-22)** and laparoscopic ovarian drilling (LOD) are used in PCOS women to induce ovulation or remove the excess ovarian stroma **(11, 23)**. Along with the classic treatment options, molecular-based therapies have offered unique opportunities for women with PCOS **(24-26)**. Long non-coding RNAs (lncRNAs) can be a potent player in the pathogenesis of PCOS **(24, 27)**. LncRNAs have crucial roles in gene transcription, cellular proliferation, inflammation, and apoptosis **(28)**. It has been reported that lncRNA metastasis-associated lung adenocarcinoma transcript-1 (MALAT1), plays an essential role in the multiple levels of gene expression and post-transcription

modification (29-31). The expression of MALAT1 was first identified in non-small cell lung cancer cells (NSCLC) (32, 33). MALAT1 as an oncogene was reported to stimulate tumor cell proliferation and migration in various cancers such as breast (34), prostate (35), stomach (36), colorectal (37), renal (38), liver (39), cervix (40), and other cancers (41, 42). Accumulating evidence has found the important roles of MALAT1 in controlling PCOS (43). MALAT1 as a competitive endogenous RNA (ceRNA) can inhibit microRNAs (miRNAs) and control granulosa cell (GCs) proliferation, apoptosis, and pathogenesis (44, 45). miRNAs are a class of ncRNAs with 20-22 lengths that regulate key genes at the level of transcription and post-transcription (46, 47). In the present article, we summarize the role of the lncRNA MALAT1/miRNA axis in PCOS.
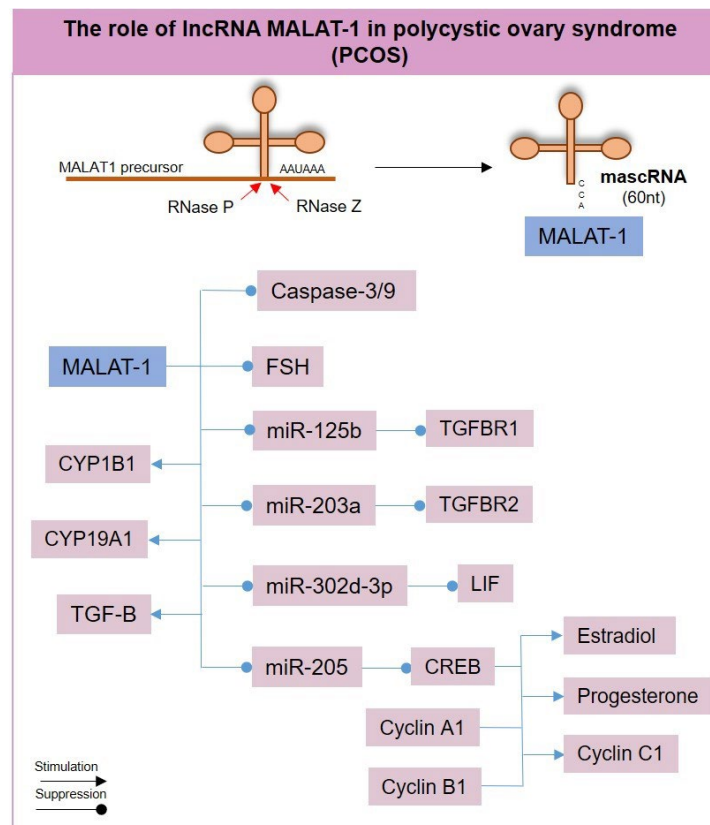
Biogenesis of MALAT1

MALAT1 or nuclear-enriched abundant transcript 2 (NEAT2) is a well-known nuclear-retained lncRNA with more than 8-kb in nuclear speckles (the sites of pre-mRNA splicing) (48). This lncRNA is transcribed via the enzyme RNA polymerase II (49) and contains a tRNA-like structure with a triple-helix element at the 3′-end known as MALAT1 associated with small cytoplasmic RNA (mascRNA) and a short poly (A) tail-like moiety (50). RNase P and RNase Z are two endonucleases that separate mascRNA and pre-mature MALAT1, respectively to produce mature-MALAT1 (51-53). MALAT1 can act as miRNA sponges and reduce the impact of miRNAs on target mRNAs (54). MALAT1 has been shown to involve in the alternative splicing of various oncogenes and the assembly of polycomb repressive complexes (PRC) such as EZH2 and SUZ12 (55). Abnormal expression of MALAT1 is one of the prognostic factors for cell autophagy, migration, and drug resistance (49, 56, 57). In the reproductive system, the abnormal expression of MALAT1 was observed in endometriosis, pregnancy loss, and PCOS (58). However, the exact function of MALAT1 in PCOS is still unclear (59). In GCs, MALAT1 has been shown to bind with miRNAs and regulate cell growth, proliferation, and apoptosis (58, 60). Table 1 and Figure 1 demonstrates a schematic of possible cross-linkages between MALAT1 and miRNAs in PCOS. Here, we summarized the functional roles of MALAT1 in GCs of patients with PCOS.

Table 1. The role of lncRNA MALAT-1 in polycystic ovary syndrome (PCOS).

MALAT-1		MALAT-1 Function	Ref.
Stimulate	**Suppress**		
TGFβ, TGFBR1, TGFBR2	**miR-125b, miR-203a**	Upregulate cell proliferation and decrease apoptosis	(61)
LIF, CYP1B1, CYP19A1	**miR-302d-3p**	Enhance proliferation and reduce apoptosis of ovarian GCs	(43)
MDM2	**P53**	Accelerated cell proliferation and decrease apoptosis	(63)
CREB1	**miR-205**	Up-regulate estradiol synthesis, decrease apoptosis and caspase-3/9 activities	(66)

MALAT1: Metastasis-associated lung adenocarcinoma transcript-1; LIF: Leukemia inhibitory factor; GCs, Granulosa cells; CREB1, Cyclic AMP response element-(CRE-) binding protein 1; E2, Estradiol; P4, Progesterone; CYP1B1: Cytochrome P450 1B1; CYP19A1: Cytochrome P450.

Figure 1. ceRNA-based MALAT-1-miRNA network in polycystic ovary syndrome (PCOS)

MALAT1 can bind with various miRNAs and regulate granulosa cell proliferation, apoptosis, and pathogenesis in PCOS.

Emerging role of lncRNA MALAT1 in GCs

Transforming growth factor beta receptor 1 (TGFBR1) and TGFBR2 are the TGF-β signaling pathway-associated genes that play pivotal roles in the pathophysiology of PCOS **(61)**. Zhang *et al.* investigated the correlation between MALAT1, miRNAs, and TGFβ on GCs from 68 patients with PCOS. They reported that low expression of MALAT1 was contributed to the disordered cell cycle and the repression of phosphor-Smad2 in the TGFβ signaling pathway. It was found that miR-125b and miR-203a (TGF-β signaling negative regulators) enhanced cell viability and proliferation, and decreased apoptosis by suppressing TGFBR1 and TGFBR2, respectively. MALAT1 as a ceRNA could interact with miR-125b and miR-203a, modulate TGFβ signaling, and regulate the cell cycle in GCs. Therefore, MALAT1 reduction may participate in the pathophysiological processes of PCOS **(60)**.

A recent study reported that low expression of MALAT1 may contribute to the pathophysiology of patients with PCOS. In GCs, MALAT1 via targeting MDM2 and PARP1 reduced p53 protein levels. Therefore, low expression of MALAT1 inhibited cell proliferation and accelerated apoptosis **(62)**.

The expression of MALAT1 was reported to be downregulated in ovarian tissue of PCOS. Chen *et al.* displayed that miR-302d-3p can suppress leukemia inhibitory factor (LIF) and increase ovarian tissue damage. MALAT1 by targeting miR-302d-3p, up-regulated the expression of LIF and reduced mouse GCs proliferation. They found that knocking down of MALAT1 accelerated the activity of caspase-3/9 and promoted cellular apoptosis. In the PCOS rat, high expression of MALAT1 decreased the concentration of FSH and enhanced estradiol (E2), T, and LH. Therefore, MALAT1 by regulating the miR-302d-3p/LIF axis has a protective role in reducing endocrine disorder in PCOS **(43)**.

Cyclic AMP response element-(CRE-) binding protein 1 (CREB1) is involved in the follicular growth and increased E2 and progesterone (P4) levels in mouse GCs. Also, the CREB1 knockdown enhanced cell proliferation and apoptosis, and decreased the expression of the Cyclin A1, Cyclin B1, and Cyclin D2 as cell cycle factors **(63)**. miR-205 by targeting CREB1 can induce GC apoptosis **(64)**. Sun *et al.* showed that MALAT1 by suppressing miR-205 positively regulates the expression of CREB1 and up-regulates the synthesis of E2 and P4. Knockdown of MALAT1 decreased estradiol synthesis, increased apoptosis and caspase-3/9 activities in mouse GCs. They also displayed that the expression of two steroidogenic enzymes such as cytochrome P450 1B1 (CYP1B1) and cytochrome P450 (CYP19A1) were decreased following MALAT1 depletion. Their results suggested that MALAT1 might be an important biomarker in the

regulation of steroidogenesis in mGCs **(29)**. Therefore, the ceRNA-based MALAT-1-miRNA network has a critical role in the pathogenesis of PCOS.

Conclusion

Considering the above-mentioned examples, we highlighted the recently reported function of MALAT1 in PCOS. Although the expression of MALAT1 was found to be decreased in women with PCOS, the exact roles of MALAT1 remain largely unknown and further studies are required to confirm this hypothesis. In GCs from patients with PCOS, MALAT1 by targeting several signaling pathways such as TGF-β, LIF, E2, P4 and some miRNAs such as miR-125b, miR-203a, miR-302d-3p, and miR-205 participates in controlling PCOS. Therefore, MALAT1 can be used as a potential biomarker for treatment of PCOS.

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Authors' contributions

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Competing interests

The authors declare that they have no competing interests.

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