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REVIEW ARTICLE

Emerging biologic and clinical implications of miR-182-5p in gynecologic cancers

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Abstract

MicroRNAs (miRNAs) have emerged as important regulators of gene expression in various biological processes, including cancer. miR-182-5p has gained attention for its potential implications in gynecologic cancers, including breast, ovarian, endometrial, and cervical cancers. miR-182-5p dysregulation has been associated with multiple facets of tumor biology in gynecologic cancers, including tumor initiation, progression, metastasis, and therapeutic response. Studies have highlighted its involvement in key signaling pathways and cellular processes that contribute to cancer development and progression. In addition, miR-182-5p has shown potential as a diagnostic and prognostic biomarker, with studies demonstrating its correlation with clinicopathological features and patient outcomes. Furthermore, the therapeutic potential of miR-182-5p is being explored in gynecologic cancers. Strategies such as miRNA mimics or inhibitors targeting miR-182-5p have shown promise in preclinical and early clinical studies. These approaches aim to modulate miR-182-5p expression, restoring normal cellular functions and potentially enhancing treatment responses. Understanding the biologic and clinical implications of miR-182-5p in gynecologic cancers is crucial for the development of targeted therapeutic strategies and personalized medicine approaches. Further investigations are needed to unravel the specific target genes and pathways regulated by miR-182-5p. It is important to consider the emerging biologic and clinical implications of miR-182-5p in gynecologic cancers.

Keywords MiRNAs · MiR-182-5p · Gynecologic cancers · Biomarker

Introduction

MicroRNAs, also known as miRNAs, are short non-coding RNA molecules consisting of approximately 22 nucleotides. They play a vital role in regulating the expression of

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numerous genes [1, 2]. It is estimated that approximately thirty percent of protein-coding genes in the human genome are influenced by miRNAs [3, 4]. miRNAs exert their regulatory function by binding to the 3′ untranslated region (UTR) of target mRNAs, leading to inhibition of expression [5]. However, there have been reports suggesting miRNA interactions with other regions, such as the 5′ UTR, coding sequence, and gene promoters [6]. Their dysregulated expression contributes significantly to the development and progression of various cancers due to their crucial role in cell development, differentiation, and cell death [7]. Consequently, their potential as diagnostic and prognostic markers is being explored. miRNAs can be classified as oncogenic miRNAs (oncomiRs) or tumor-suppressor miRNAs, and the development of cancer is often associated with either the overexpression of oncomiRs or the downregulation of suppressor miRNAs [8].

Gynecologic cancers (GCs) are the most prevalent type of cancer among women, affecting organs such as the ovaries, breast, endometrium, cervix, and vulva. Several factors contribute to the challenges in diagnosing GCs, including complex pathogenesis, disease heterogeneity, and diagnostic difficulties [9].

miR-182 regulates multiple target genes and signaling pathways and exhibits a dual role in different tumor types [10]. miR-182 is part of the miR-183/96/182 cluster, which is highly conserved in vertebrates and located within 4 kilobases (kb) on mouse chromosome 6qA3, with conservation of synteny and order to human chromosome 7q32.2 [11]. These miRNAs are transcribed from a single primary transcript and exhibit similar expression patterns during development [12]. miR-182-5p plays a critical role in the normal differentiation of sensory organs (such as the retina, nose, and inner ear), immune system function, lymphatic vessel development, bone health, and the development of various diseases, including autoimmune diseases, tumors, metabolic disorders, and depression [12–14]. This miRNA has been reported to regulate cancer-related processes such as apoptosis, DNA repair, angiogenesis, epithelial to mesenchymal transition (EMT), cell motility, and invasion [15, 16].

Gynecologic cancers (GCs) are the most prevalent type of cancer among women, affecting organs such as the ovaries, breast, endometrium, cervix, and vulva. Several factors contribute to the challenges in diagnosing GCs, including complex pathogenesis, disease heterogeneity, and diagnostic difficulties [9]. The implications of miR-182 in GCs are significant and offer valuable insights into the pathogenesis and potential therapeutic strategies for these malignancies. Its aberrant expression is associated with tumor initiation, progression, and metastasis. In some cases, miR-182 acts as an oncogenic miRNA, promoting tumor growth, angiogenesis, and invasion by targeting tumor suppressor genes and key signaling pathways. Conversely, in certain contexts, miR-182 may function as a tumor-suppressor miRNA, inhibiting cell proliferation and inducing apoptosis. The differential expression and dual role of miR-182 in GCs highlight its potential as a diagnostic biomarker and therapeutic target.

Insights for miRNAs-targeted therapeutics

Numerous studies indicate two primary strategies for targeting miRNA in cancer: direct and indirect approaches. Direct methods involve using viral vectors or oligonucleotide-based constructs. These techniques aim to either inhibit the expression of oncogenic miRNAs or to restore the expression of tumor-suppressor miRNAs that may be lost in malignancy [17]. The observation that oncogenic miRNAs are overexpressed in cancer has provided a basis for considering the use of antisense oligonucleotides to inhibit miRNA expression [18]. Antisense oligonucleotides act as competitive inhibitors of miRNAs by binding to the mature miRNA guide strand. This binding promotes the formation of stable duplexes or accelerates the degradation of the miRNA, effectively reducing its activity and impact on gene regulation [19]. In addition, locked nucleic acid (LNA) oligonucleotides exhibit remarkable hybridization properties due to the presence of a methylene bridge that blocks certain molecular interactions. This modification allows them to bind effectively to complementary single-stranded RNA, as well as to both single- and double-stranded DNA, demonstrating a unique dependency in their hybridization behavior [20]. Furthermore, LNA oligonucleotides exhibit significant differences in their ability to tolerate mismatches, along with excellent solubility in aqueous environments. As a result, LNA anti-miRNA constructs have been successfully utilized in numerous in vitro studies to selectively inhibit the expression of specific miRNAs [21]. miRNA sponges, along with a new technology known as miRNA-masking antisense oligonucleotides, can serve as effective screening tools for identifying small molecules that act as suppressors of various oncogenic miRNAs [22]. These insights can be integrated with traditional cancer treatment methods to develop promising combinatorial strategies for therapy [17]. The absence or reduced expression of a tumor-suppressor miRNA can be effectively addressed by introducing synthetic oligonucleotides known as miRNA mimics [23–25]. Another strategy for promoting the expression of tumor-suppressor miRNAs in cancer involves the use of adeno-associated virus (AAV) vectors [26]. So far, all strategies aimed at regulating miRNA expression have focused on targeting either a single miRNA or a specific family of miRNAs [27]. Given that miRNAs are believed to play a significant role in malignant carcinogenesis and that their phenotypic effects arise from complex interactions with the transcriptome, it makes sense to explore strategies aimed at reconfiguring abnormal miRNA

networks in cancer [17]. Reprogramming can be achieved by regulating key miRNAs involved in a specific network using mimics or antisense oligonucleotides. However, targeting multiple miRNAs with these methods can present technical challenges [28–30]. An alternative approach to modulating miRNA expression involves indirect methods. These techniques utilize drugs to regulate miRNA transcription and processing, rather than directly targeting the mature miRNA itself. By manipulating the cellular machinery responsible for miRNA biogenesis, indirect approaches can influence the expression of multiple miRNAs simultaneously, potentially leading to broader therapeutic effects.

The role of mir-182-5p in cancerous and non-cancerous diseases

During the biogenesis of miRNAs, two pathways are involved: the canonical pathway and the non-canonical pathway. The canonical pathway is the predominant pathway for miRNA biogenesis. The process begins with the transcription of miRNA genes by RNA polymerase II (Pol II) in the nucleus, resulting in the generation of primary miRNAs (pri-miRNAs). These pri-miRNAs undergo capping, splicing, and polyadenylation. Approximately 30% of miRNAs are derived from introns of protein-coding genes, while the majority of other miRNAs are expressed from specific miRNA gene loci [31].

The long pri-miRNAs are then cleaved by a complex called microprocessor, which consists of two key components, DROSHA and DiGeorge syndrome critical region 8 (DGCR8). This cleavage generates precursor miRNAs (pre-miRNAs) that are approximately 60–70 nucleotides in length. The pre-miRNAs are subsequently exported from the nucleus to the cytoplasm with the help of exportin 5 (XPO5). In the cytoplasm, the pre-miRNAs undergo further processing by an enzyme called DICER1, which is a ribonuclease III (RIII) enzyme. DICER1 cleaves the pre-miRNAs, leading to the production of mature miRNAs. The guide strand of the mature miRNA is then loaded into the miRNA-induced silencing complex (miRISC), which is composed of DICER1 and Argonaute (AGO) proteins. The miRISC, guided by the miRNA, recognizes and binds to target mRNAs through sequence complementarity. This binding mediates gene suppression through mechanisms such as mRNA degradation and translational blocking. These processes often occur in specialized structures called processing bodies (P-bodies) [32] (Fig. 1).

miR-182-5p has been proven to be related to various cancers. However, miR-182-5p's role is complicated depending on the malignancy. It may act as a tumor suppressor or an oncogene. miR-182-5p functions as a tumor

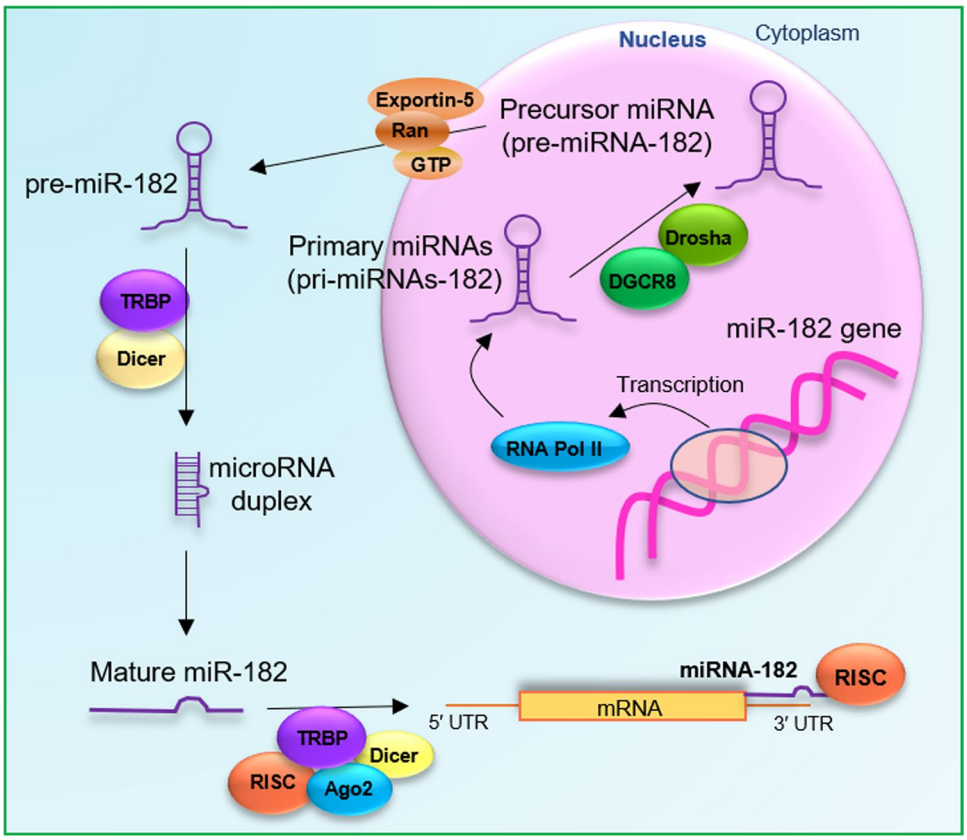

Fig. 1 Biogenesis of miR-182-5p. miR-182-5p is a mature miRNA that is derived from the precursor miRNA, pre-miR-182. The biogenesis of miR-182-5p involves transcription, nuclear processing, nuclear export, cytoplasmic processing, RISC loading. Targeting these pathways may provide novel therapeutic opportunities for the management of gynecologic cancer

suppressor in glioblastoma and renal cell carcinoma (RCC) [33], and non-small cell lung cancer (NSCLC) [34] and is recognized as onco-miR in melanoma, ovarian cancer, breast cancer, and prostate cancer.

Dysregulation of miRNAs may have a role in several diseases besides cancer. For example, there is evidence that miR-182-5p protects against liver ischemia–reperfusion and cerebral ischemia–reperfusion injuries. By targeting toll-like receptor 4 (TLR4), an intrinsic immune signaling receptor, miR-182-5p inhibits the release of proinflammatory cytokines, including IL-6 and TNF-α, to protect against the side effects of liver and cerebral ischemia–reperfusion injuries, such as suppression of the inflammatory response [35]. Using miR-182-5p mimic inhibits the pathogenic Th17 response in experimental autoimmune uveitis (EAU) mice. miR-182-5p's inhibition of TATA-binding protein-associated factor 15 (TAF15, TAFII68) negatively regulates Th17 cell development by suppressing STAT3 phosphorylation. Considering the positive relationship between TAF15 and Th17 cell markers in uveitis patients, the miR-182-5p/TAF15 axis may have therapeutic potential for uveitis [36]. Another study demonstrated the therapeutic potential of hypoxic mesenchymal stromal cells-Exo (Hp-Exo) in liver regeneration, demonstrating that miR-182-5p from Hp-Exo facilitates macrophage polarization during liver regeneration by modulating FOXO1/TLR4 signaling pathway [37]. Compared to the healthy population, the plasma of individuals with coronary atherosclerosis expressed less miR-182–5p. While the content of serum pregnancy associated plasma protein A (PAPPA) was significantly increased, and the expression level of miR-182-5p was negatively correlated with the PAPPA content. PAPPA could promote the activation of IGF signaling pathway in human aortic smooth muscle cells (HA-VSMC) treated by oxidized low-density lipoprotein (ox-LDL), further activate NFkB, PI3K/AKT and ERK signaling pathway, and promote cell proliferation. miR-182-5p could target the 3'-UTR of PAPPA to inhibit its expression. This approach might offer new non-invasive diagnostic information as well as possible therapeutic targets for cardiovascular disease treatment [38]. It has been shown that patients with lupus nephritis (LN) had higher expression of miR-182-5p, which may have contributed to the inhibition of FOXO1 and the development of LN [39]. miR-182-5p inhibitors exerted protective effects against colitis induced by dextran sodium sulfate (DSS). The protective effects included improvements in pathological changes, increased anti-inflammatory and anti-oxidative genes, and upregulation of TGF-β1. Claudin-2 mRNA was predicted as the miR-182-5p target [40]. Generally, miR-182-5p is considered an important miRNA in human cells' normal functioning.

Functional roles of miR-182-5p in gynecologic cancer

Breast cancer

miRNAs are expressed in an altered pattern among breast tumors. The miRNA dysregulation is associated with different pathological directions in the breast cancer (BC). Almost all molecular aspects of the BC are influenced by aberrant miRNA regulation [41]. Interestingly, specific dysregulated miRNA clusters have been indicated in BC so far making therapeutic manipulation of the predominant miRNAs more feasible and efficient [42]. The administrative significance of miR-182 in BC progression has been uncovered since a couple of years ago. Conventionally, it is believed that miR-182 is overexpressed in BC cells and employs oncogenic properties through targeting different genes. miR-182 is highly expressed in triple-negative BC (TNBC) tissues compared to the normal counterparts [43]. In vitro neutralization of miR-182 resulted in diminished BC cell growth, proliferation and invasion, and increased apoptosis [44]. Lei et al. discovered the inhibitory effect of miR-182 on missing in metastasis (MIM) gene in BC cells, which leads to increased BC cell migration and metastasis [45]. MIM suppresses metastasis via inhibition of Ras homolog family member A (RhoA) and stress fiber synthesis in BC. Wo and colleagues investigated the association of miR-182 and TNF-α exposure in TNBC cells and found that knockdown on miR-182 leads to upregulation of CYLD deubiquitinase and removal of ubiquitin chains from receptor interacting protein kinase 1 (RIP1) protein [46]. The consequence is increased TNBC cell apoptosis mediated by caspase 8 activation in the cells treated with TNF-α. Moreover, Sharifi et al. blocked the miR-182-5p activity in BC cells by locked nucleic acid and found increased level of caspase 9 and apoptosis [47]. miRNA-182 overexpression also leads to increased BC proliferation and regulation of actin distribution and filopodia formation which enhances BC invasiveness and metastasis. E3 ubiquitin-protein ligase member FBXW7 is repressed by miR-182. Therefore, upregulated miR-182 increases HIF-1α and, in turn, VEGF-A expression levels facilitating BC progression and tumor vessel formation [48]. Moreover, Wu et al. depicted another impression for FBXW7 suppression by miR-182-5p in TNBC cells. In vitro assays revealed that the inhibitory function of miR-182-5p brings about TLR-4/NF-κB pathway overactivity and elevation in IL-1 β, IL-6, IL-18, and TNF-α levels which results in TNBC cell division and migration [49]. Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is a potent tumor suppressor in multiple cancer types like BC and is a target for a couple of miRNAs. Zhao et al.

demonstrated that miR-182-5p could effectively target PTEN mRNA in BC cells and the repression of its activity as correlated with diminished BC progression [50]. Breast cancer cell viability and chemoresistance is promoted by miR-182. It was recently reported by Wan et al. that STAT5 binds to the promoter of miR-182 causing its overexpression in BC which leads to the drug resistance. NOD-like receptor family pyrin domain-containing 3 (NLRP3) is neutralized by miR-182. Thus, silencing the expression of STAT5 reduces miR-182 level and increases drug sensitivity and pyroptosis, form of cell death mediated by inflammation, via NLRP3 [51]. The context of transferring non-coding RNAs especially miRNAs by extracellular vesicles (EVs) in the cancer biology and development has drawn attention in recent years [52]. Chemokine-like factor like MARVEL transmembrane domain-containing 7 (CMTM7) is a molecule with cancer-repressing function which is downregulated in many tumors. It is believed that CMTM7 suppresses EGFR/AKT oncogenic pathway. Lu et al. found that miR-182-5p is highly enriched in BC cells and could be transmitted by the EVs and augment proliferation, migration and angiogenesis in the receiver cells. They also reported that CMTM7 is a target for miR-182-5p in the BC cells. Therefore, influencing CMTM7/EGFR/AKT axis is the underlying mechanism [53]. In a latter investigation by Chen and colleagues, CMTM7 was revealed to be regulated via miR-182-5p and promoter methylation in BC. Wnt/β-catenin pathway suppression was the reported process for CMTM7 activity. Also, as an upstream regulator, transcription factor 3 was suggested to enhance miR-182-5p [54]. Tumor-associated macrophages (TAMs) are of principal members in the tumor tissue which modulate tumor immunity in a binary manner. According to polarization status of the TAMs, they may induce or suppress antitumor immunity (M1vs M2 polarization, respectively). Recently, Ma et al. demonstrated that overexpression of miR-182 in TAMs residing BC tissues leads to M2 polarization that direct neutralization of miR-182 in TAMs by the means of EVs carrying the antagonist impairs BC progression. TGF-β released from BC tumor cells upregulates miR-182 in TAMs nearby. miR-182 then inactivates NF-κb and facilitates M2 polarization via targeting toll-like receptor 4 (TLR-4) gene [55]. Current research considers the upstream regulators of miR-182 in parallel to its target pathways in BC. Tumor cell plasticity and mobility is a key capacity for the solid cancers to migrate and metastasize and to gain mesenchymal features is an early step. Transforming growth factor-β (TGF-β) is the main mediator of this process partly through TGF-β/SMAD pathway. Basal-like breast cancer (BLBC) tends to acquire mesenchymal capability more easily. It is shown that FOXF2 downregulation and miR-182-5p upregulation are correlated with higher invasive and migratory potential in BLBC. Lu et al. revealed that miR-182-5p targets FOXF2 and represses its expression and TGF-β is an effector to increase miR-182-5p in BLBC cells. In other words, TGF-β/SMAD/miR-182-5p acts to silence FOXF2 in BLBC cells to enhance the metastatic potential [56]. Sang et al. attempted to study the effect of circRNAs in non-responsiveness to tamoxifen in BC cells. Using RNA seq techniques, they found that hsa-circ-0025202 is significantly downregulated in tamoxifen-resistant BC cells that its enrichment could limit BC colony formation, migration, and tamoxifen resistance. They also reported that this circRNA sponges miR-182-5p which targets the tumor-suppressor FOXO3a implying an anticancer impact. Thus, miR-182-5p/FOXO3a axis is regulated by hsa-circ-0025202 [57]. Hsa-circ-0007823 also depicts diminished expression in TNBC cells according to a study by Yu and co-workers. The tumor suppressive effects of hsa-circ-0007823 such as reducing TNBC cell viability and migration as well as apoptosis induction were found to be associated with miR-182-5p/FOXO1 axis modification in which the circRNA neutralizes miR-182-5p making the activity of FOXO1 more probable [58]. Forkhead-box O 1 (FOXO1) is a relatively well-known target for miR-182-5p with tumor suppressor impacts in many cancers [59]. Moreover, lncRNA MALAT-1 has been suggested as a potential sponger of miR-182 in TNBC cells and its silencing leads to increased mesothelin transcripts [60]. Also, lncRNA SLC16A1-AS1 interferes with the function of miR-182 in targeting programmed cell death 4 (PDCD4) in TNBC tissues. SLC16A1-AS1 and PDCD4 upregulation stopped the progression of cell cycle from G1 to G2 phase restraining TNBC cell proliferation while miR-182 overexpression depicted opposite outcome [61].

Intriguingly, more recent studies have further broadened our horizon about the roles of miR-182 in BC with some contradictory results. According to an in vitro plus in vivo study, inhibition of MET gene by miR-182 has introduced an anticancer mechanism which enhances trastuzumab sensitivity in $HER2^+$ BC cells and decreased viability and invasion. MET is a receptor tyrosine kinase protein which mediates trastuzumab resistance in BC via the PI3K/AKT/mTOR pathway [62]. Among the cardinal molecules which maintain cancer cell viability and proliferation capacity is telomeric repeat-binding factor 2 (TRF2) which preserves telomere structure and function. Dinami and co-workers reported that miR-182-3p is an efficient post-transcriptional regulator for TRF2 through in silico and in vivo investigations. MicroRNA-182-3p overexpression leads to telomeric and pericentromeric DNA damage and apoptosis. Lipid nanoparticles embedded with miR-182-3p introduced to TNBC xenograft mouse models impaired tumor growth both at the primary site and brain bringing a novel promising data about the therapeutic impression of miR-182-3p [63].

Clinical prospects

Interestingly, the expression and biological activity of miR-182 could also interfere with clinical and clinicopathological aspects of BC. An in silico database mining by Murugesan et al. brought miR-182 a prominent miRNA with significant differentially expression in BC tumor tissue and participation in different biologic pathways. The expression of miR-182 was significantly correlated with estrogen receptor and attentively related to progesterone receptor and HER2 positivity. Furthermore, miR-182 was associated with unfavorable patient prognosis [64]. Larger tumor diameter, advanced pathological grading, and TNM staging were all correlated with higher miR-182 expression among the BC patients in another study by Kandil et al. [65]. Since CMTM7 is regulated by miR-182-5p, low levels of tumor tissue CMTM7 were correlated with diminished overall survival (OS) time [54]. Tumor suppressors BRCA1 and BRCA2 are two major genes involved in the homologous recombination (HR) during DNA double-strand break (DSB) damage; thus, their germline mutation and loss of function are associated with DNA repair errors and increased BC tumorigenesis. The term "BRCAness" indicates sporadic mutations in genes participating in the HR and DSB repair. A variety of genes involved in HR process are potential targets for miR-182-5p. Darbeheshti et al. reported that plasma and tumor levels of miR-182-5p represent positive correlation. Therefore, they hypothesized that cell-free miR-182-5p could predict the BRCAness facilitating selection of the precise targeted treatments. They also revealed that TNBC patients had higher plasma miR-182-5p. Tumor tissue miR-182-5p overexpression was related to larger size and higher histologic grade and more positive lymph nodes among the patients, as well [66]. Aiming to mimic the precancerous state, Naser Al Deen and colleagues silenced and deactivated gap junction family member Cx43 which led to loss of polarity in normal mammary epithelium. Among the multiple dysregulated miRNAs and circRNAs obtained from microarray profiling, only the Cx43/hsa-circ-0077755/miR-182 axis, in which Cx43 enhances the circRNA repressing the miR-182 activity, showed the capability to predict BC initiation [67]. Eventually, the study by Mansouri et al. indicates the impact of miR-182 rs4541843 genotype in BC incidence and characteristics. They discovered that abundance of GG + AG genotypes has significant correlation with the occurrence of BC compared to AA. Furthermore, the genotypes AA and AG could decrease the BC initiation risk. Accordingly, they suggested that rs4541843 variant may affect maturation process of the miR-182 inhibiting its oncogenic function [68]. However, this finding has to be generalized and validated in other ethnic groups since this study included only Iranian patients.

Ovarian cancer

Extraordinary inquiries in the field of experimental and clinical aspects of ovarian cancer (OC) biology and treatment have brought heartening outcomes in recent years. Precise targeted therapeutics, especially those considering the genetic dysregulation in cellular level, are emerging to replace the conventional approaches [69]. Many in vitro models such as 2D cultures as well as 3D spheroids and organoids which may include stromal elements have been introduced to better develop individualized treatments and overcome the drug resistance [70]. RNA dysregulation seems to act as a remarkable determining factor in the landscape of OC. The outline of specific RNA molecules in platelets from the OC patients could affect the disease fate [71]. Similar to almost every other tumor type, altered expression characteristics of miRNAs influence the key biologic properties of the OC like cell cycle control, apoptosis, and cellular mobility. Diverse miRNA profiles could be a tool to distinguish malignant cells and is associated with tumor histological features and clinical stage [72]. Recently, Beg et al. conducted an in silico study that revealed five upregulated and five downregulated gene candidates to discover pivotal miRNAs in OC. Beg et al. concluded that miR-660-5p could be considered as a principle downregulated miRNA and miR-18a-5p, miR-187-3p, and miR-182-5p as major upregulated ones in the human OC samples [73]. Of most frequent miRNAs with deregulated expression in OC especially in the epithelial type (EOC) is miR-182. By targeting programmed cell death 4 (PDCD4) and breast cancer 1 (BRCA1) genes, it exerts an oncogenic effect and facilitates OC progression. Marzec-Kotarska and colleagues demonstrated the significant higher expression levels of miR-182 in human EOC tissues. Aiming to determine the underlying mechanism, they suggested increased copy numbers in the miR-182 coding sequences and deletion in PR/SET Domain 5 (PRDM5) gene as two independent factors. However, the miR-182 gene promoter was found to be generally hypomethylated in the EOC samples, either. Interestingly, patients with higher tissue expression of miR-182 depicted more limited survival time [74]. It is worth noting that the copy number gain had been previously suggested as the causal mechanism for miR-182 overexpression in EOC [75]. The bioinformatic exploration and literature review conducted by Li et al. brought the results indicating high levels and essential tumor-promoting biological roles of miR-182 in OC [76]. Záveský et al. revealed that miR-182-5p, among other miRNA candidates, is highly expressed in OC tumor samples and ascitic fluid of the OC patients. miR-182-5p also depicted enhanced levels in high-grade tumors. Using ROC curve creation, tissue and ascites fluid miR-182-5p showed a remarkable sensitivity and specificity to distinguish the patients from controls [77]. High Mobility

Group A (HMGA) is an oncofetal gene which plays considerable roles in fetal development and tumor progression. High HMGA levels positively regulate multiple cancer types including OCs and is correlated with more aggressive features. High-grade serous OC (HGSOC) is characterized by BRCA1 mutation/inactivation and elevated miR-182 expression. Due to the fact that miR-182 represses BRCA1, this mechanism has been proposed as a mediator for HMGA upregulation. Also, by enhancing the expression levels of miR-182 and HMGA in normal ovarian epithelial cells and malignant cell lines, they demonstrate increased cancerous transformation and invasive behavior, respectively [78, 79]. Sathipati et al. performed a bioinformatic investigation to develop miRNA signature in OC patients. Among the upregulated miRNAs, miR-182 in parallel to some other ones (e.g., miR-34a and miR-342) was enriched in fatty acid synthesis pathway. In general, fatty acid biosynthesis pathway overactivation is found to facilitate OC progression [80].

Regulatory axes for miRNAs have attracted the attention of many cancer researchers. Long non-coding RNAs (lncRNAs) and circRNAs are two prominent molecules harboring the potential to sponge and neutralize miRNAs. Wang et al. reported that circRNA MTO1 is downregulated in OC tissues and its overexpression is associated with diminished OC cell proliferation and invasion. MicroRNA-182-5p was introduced as the target for this circRNA which exerts the oncogenic features by repressing KLF15 gene. Thus, the circMTO1/miR-182-5p/KLF15 pathway is a likely tumor-repressing machinery in OC [81]. Furthermore, miR-182-5p serves as the regulator of FOXF2 gene resulting in OC proliferation, mobility, and invasion. LncRNA ADAMTS9-AS2 is another competing RNA for miR-182-5p which could reverse its oncogenic effects by suppressing the miR-182-5p/FOXF2 axis [82].

Besides the cancer-promoting impressions of miR-182 in the literature, some researches have indicated its antitumor activities [83]. Ramalho et al. demonstrated that high levels of discoidin domain receptor 2 (DDR2; a kinase protein which mediates cell–ECM interaction) in the HGSOC tissues correlates with higher FIGO stage, CA125 level, and residual disease following tumor resection bringing unfavorable prognosis. Intriguingly, the expression of miR-182 was lower in tumors with elevated DDR2 suggesting an inverse relationship between miR-182 level and patients' survival [84]. In addition, Duan and colleagues hypothesized that miR-182-5p may modulate cisplatin resistance of the OC cells due to the same regulatory role of this miRNA in lung and bladder cancer. They found that miR-182-5p has diminished expression levels in OC tissues and cell line. Increased levels of miR-182-5p resulted in enhanced cisplatin sensitivity in the resilient OC cells as well. They also revealed that cyclin-dependent kinase 6 (CDK6) acts as mediator for OC cisplatin resistance and is targeted by miR-182-5p. These data indicate the potential tumor-suppressive characteristics of miR-182-5p in OC [85]. However, in a previous study by Li et al., miR-182 had been reported to be significantly upregulated in cisplatin-resistant OC cell line A2780/DDP [86]. Lu et al. also reported lower levels of miR-182 in the OC tumors caused by DNA (cytosine-5)-methyltransferase 3α (DNMT3a). Their investigation revealed the positive impact of miR-182 on OC cell apoptosis suggesting additional contradictory evidence related to the roles of miR-182 in the OC tumorigenesis [87].

Clinical prospects

Considering the clinical implications of miR-182 in the OC landscape, Meng et al. aimed to explore the capacity of seven circulating miRNAs including miR-182 to determine the patients' clinicopathological features. But in contrast to the other candidate miRNAs, miR-182 levels depicted no significant statistical distinction between the case and healthy cohorts [88]. However, the low expression of miR-182 target genes among OC samples is correlated to limited patient survival period [76]. Eventually, in a recent fascinating paper, Elias et al. introduced a serum miRNA profile comprising ten candidates including miR-182-5p which was able to separate the cases as probable or unlikely to bear a BRCA1/2 mutation with acceptable sensitivity and specificity. This model could be utilized to apply more focused screenings on the individuals at the high risk of heritable ovarian and breast cancer [89].

Cervical cancer

Almost all cervical cancer (CC) cases suffer chronic HPV infection before the malignant transformation begins and the cancer is clinically detectable. However, not all HPV-infected women develop CC indicating the presence of other regulatory machineries. MicroRNAs play major roles, and they are aberrantly expressed in the way from the low-grade cervical squamous intraepithelial lesion to invasive cervical cancer. They could either facilitate CC progression or suppress its development [90]. Data from the studies since almost a decade ago depict contrasting roles and functions for miR-182 in the CC biology. A relatively incipient study by Tang et al. showed that miR-182 is overexpressed in primary CC tissues compared to the normal cervical cells and its expression amount positively correlates with the cancer stage. Inhibition of miR-182 in xenograft models resulted in tumor shrinkage and growth suppression. The authors also speculated that miR-182 is involved in the apoptosis pathway and three potential miR-182 target genes—Rap guanine nucleotide exchange factor 4 (RAPGEF4), chromobox homolog 2 (CBX2), and FOXO1 were suggested [91]. In addition, the in vitro exploration by Li and colleagues using

CC HeLa cell line demonstrated that liposome-based transfection of the CC cells with miR-182 causes increased proliferation rate. They also discovered that miR-182 acts via targeting the tumor-suppressor adenomatous polyposis coli (APC) mRNA which leads to upregulation of Wnt pathway downstream mediators (e.g., c-Myc and cyclin D1) [92]. Also, supporting the previous finding, it was uncovered that miR-182 could promote Wnt/β-catenin axis and upregulate its downstream mediators leading to CC development [93]. Previous data also elucidate the crosstalk between HPV viral genes and miR-182 expression. It is believed that E7 oncoprotein from high-risk HPV types attaches the tumor-suppressor pRb and facilitates cell proliferation. It is revealed by Chen et al. that following the high-risk E7-pRb complex formation, TGF-β is upregulated in cervical cells. Consequently, Smad4 pathway is activated which enhances miR-182 level via interaction with its promoter region. Therefore, high-risk HPV E7/TGF-β/Smad/miR-182 axis could be mentioned as a regulation machinery for miR-182 during CC tumorigenesis [94]. Javadi et al. studied the impact of miR-182 inhibition along with repression of E6 and E7 on the viability of $HPV16^+$ CC cells. They concluded that miR-182 neutralization reduced the CC cell viability partly through p21 and FOXO1 overexpression and apoptosis induction. Combined administration of E6/E7 inhibitor and anti-miR-182 led to more limited CC cell viability. While, simultaneous utilization of anti-miR-182 and cisplatin depicted no significant effect on the CC cell viability reduction [95]. F-box and WD repeat domain-containing 7 (FBXW7) gene mRNA is also repressed by miR-182-5p in the CC cells. According to the study by Zhang and coworkers, miR-182-5p/FBXW7 axis is regulated by lncRNA LINC00173 which sponges and deactivates the miRNA. The outcome is inhibition of CC cell division and invasive potential [96]. Recently, the significance of miR-182-3p in the CC biology has been elucidated through bioinformatic approaches. The results indicated that miR-182-3p is highly expressed among CC tissues compared to normal cervical samples. The suggested most reliable target gene was FLI-1 which is known to bear oncogene or tumor-suppressive features in diverse cancers. However, the miR-182-3p activity is not the only regulation mechanism for FLI-1 in CC. FLI-1 play roles in the immune response pathways and its downregulation is associated with decreased immune cell recruitment in CC [97].

In contrast, Sun et al. reported that miR-182 is lowly expressed in CC tissue than the non-malignant adjacent counterpart. Transfection of CC cells with miR-182 led to apoptosis promotion and cell death. The underlying reason for that was DNA methyltransferase 3a (DNMT3a) inhibition that its administration to CC cells brought diminished miR-182-nduced apoptosis, consequently [98]. In the study by Zhang et al. intended to reveal upstream regulator of miR-182 activity in CC, they reported that miR-182/FBXW11 axis is deactivated by lncRNA PCGEM1, the outcome of which is CC cell proliferation and invasion. Therefore, this study proposes antitumor implication for miR-182 through FBXW11 inhibition. FBXW11 promotes CC development by activating NF-κB and β-catenin/TCF signaling machineries [99].

Clinical prospects

Some studies indicated the potential of miR-182 or its upstream/target molecules to determine the clinical characteristics of CC. However, there is a long way to go to reach applicable results. Okoye et al. reported that the serum miR-182 significantly correlates with the tumor tissue levels in CC patients and the amount of circulating miR-182 is higher in more severe CC types. Also, individuals with precancerous lesions depicted elevated blood miR-182 compared to the healthy counterparts [100]. As suggested by Gao et al., higher tissue miR-182 may significantly correlate with CC lymphatic metastasis. While, it was not associated with FIGO stage, tumor size, or vascular invasion [93]. Tumor miR-182-3p expression did not influence patients' OS; even though, lower tissue FLI-1 (as the target for miR-182-3p) was correlated with reduced recurrence-free survival time [97]. Finally, the expression of lncRNA PCGEM1, which neutralizes miR-182, was significantly associated with limited OS period [99]. These data imply the indirect impact of miR-182 activity or its modification on the patient prognosis.

Endometrial cancer

Dysregulated miRNAs bear undeniable roles in endometrial cancer (EC) progression. Large amounts of proportionally up- and downregulated miRNAs have been introduced in EC tissues which alter the biology of pathways related to survival, inflammation, and chromatin remodeling. Among the overexpressed effector miRNAs, miR-182 with modified locus methylation may be the one with considerable impacts which is worth focusing on [101]. It has been elucidated for more than a decade that aberrant miRNA profile in EC tissues causes uncontrolled cell division and impaired apoptotic response. As discussed in other gynecologic cancers, FOXO1 gene exerts anticancer impressions in EC via cell cycle arrest induction and increasing vulnerability to therapeutic agents. Among other upregulated miRNAs, miR-182 is a suppressor for FOXO1 that contributes to EC progression [102]. Guo et al. described upregulation of miR-182 in EC cells compared to the normal counterparts. Overexpressed miR-182 was associated with high levels of EC proliferation and colony formation. They also reported transcription elongation factor A-like 7 (TCEAL7) as a target for miR-182. The repression of tumor-suppressor TCEAL7

enhances downstream proliferative genes cyclin D1 and c-Myc and activates NF-κB signaling [103]. The cullin-RING E3 ubiquitin ligase family member cullin 5 (CUL-5) takes part in cell cycle and cell proliferation pathways and has got antiproliferative impacts that its reduced expression is predictable in cancers. It is found in a study by Devor et al. that CUL-5 is downregulated by miR-182 in EC cells; the outcome of which is increased EC cell proliferation. Cullin 5 repression may lead to elevation in the level of its client proteins JAK2 and FasL that have pro-growth effects. Interestingly, the miR-182 promoter regions were reported to be unmethylated in the EC cells [104]. The confirming data about the pro-tumor activity of miR-182 were obtained from the study conducted by Yao and colleagues. They revealed that miR-182 overexpression in EC cells is correlated to increased cell proliferation, invasion, migration, and EMT happened following FOXF2 suppression. miR-182 inhibition or FOXF2 upregulation led to G1 cell cycle arrest in the EC cells, suggesting a potential manipulation landscape [105]. The activity of STAT proteins as part of the JAK-STAT pathway leads to tumor promotion. Protein inhibitor of activated STAT (PIAS) proteins impede STAT proteins in diverse cancer types like EC. According to the investigation by Xiao et al., bioinformatic investigation confirmed by in vitro assay showed that both miR-182-5p and miR-96-5p target PIAS1 in EC. Also, PIAS1 downregulation led to STAT3 activation and miR-182-5p and miR-96-5p overexpression indicating the fact that these two miRNAs mediate the negative regulatory feedback loop between PIAS1 and STAT3 [106]. A bunch of studies have reported that miR-182 is also a regulator for PTEN gene. However, Nishijima et al. have recently observed that miR-182 and PTEN do not depict obvious inverse correlation in EC tissues. Their study also concluded that miR-182 has remarkable positive correlations with miR-183, miR-200a, and miR-200b which may suggest similarity between pathways in which the miRNAs take part [107]. The functional role of miR-182 sounds to be different in endometriosis in comparison with EC biology. Wu and Zhang demonstrated that miR-182 is downregulated in the ectopic endometrial tissues. According to them, miR-182 represses protooncogene RELA and inhibits the proliferation, invasion, migration, and EMT capacity in the endometrial cells via deactivation of NF-κB pathway [108].

In addition to promoter hypomethylation, there are other regulation mechanisms for miR-182 in EC. LnRNAs and circRNAs bear the potential to sponge and deactivate miR-182 and alter the EC characteristics. LncRNA LINC00261 demonstrates low expression levels in solid cancers including endometrial carcinoma. Fang et al. explored the impact of LINC00261 activity in EC and discovered miR-182 suppression as a consequence. They also reported that LINC00261 inhibits EC cell proliferation, invasion, and metastasis through the rescue of FOXO1 from being targeted by miR-182 [109]. Similarly, circ-0001776/miR-182/LRIG2 is another functional axis in which circ-0001776 sponges miR-182 to enhance the function of leucine-rich repeats and immunoglobulin-like domains 2 (LRIG2) gene. Normally, circ-0001776 is lowly expressed in EC cells and its escalated expression results in attenuated proliferation and glycolysis and raised apoptosis through LRIG2 freeing from miR-182-mediated neutralization [110]. Figure 2 illustrates the upstream and downstream targets related to the regulation of miR-182-5p in gynecologic cancers.

Clinical prospects

The expression status of miRNAs could determine the patient-related aspects of EC as seen in other gynecologic tumors. Given that miR-182 is an upregulated one with generally oncogenic roles, it would be reasoning to anticipate clinical implications for this miRNA [111]. Tissue levels of miR-182 along with other onco-miRNAs have depicted capacity to distinguish patients and normal non-malignant conditions. In a study by Lee et al., the expression levels of a panel consisted of six miRNAs miR-21, 182, 183, 200a, 200c, and 205 could differentiate EC cases from endometrial hyperplasia and normal-endometrium individuals with the sensitivity and specificity of 91% and 94%, respectively. While the miR-182 level alone only demonstrated moderate potential with 64% sensitivity and 91% specificity. Also, the capability of miR-182 to discriminate EC and complex atypical hyperplasia was not very remarkable (81% sensitivity and 73% specificity) [112]. Eventually, the expression of miR-182 may be inspected in a subtype-specific manner that previous papers have reported the endometrioid subtype to bear higher miR-182, whereas serous type EC did not outline that significant overexpression [113].

It is obvious that miRNAs function in molecular networks and may potentially take part in diverse axes in which one or more gene is regulated and the miRNA itself could be a target for other regulatory mediators. To realize these networks and their crosstalk makes it easier to develop modifier agents and alter the impacts of the miRNAs more efficiently [114, 115]. As mentioned earlier in this review, there are regulatory pathways for miR-182 or its subfamilies in different kinds of gynecologic cancers. Table 1 summarizes the indicated machineries and their outcomes. Although it is conventionally believed that miR-182 and its subfamilies promote the gynecologic cancers' progression. This data is valuable due to the broader potentially practical information for the future research. Summarized information about antitumor impacts of miR-182 is reachable in Table 2 and Fig. 3.

Several strategies are being explored to eliminate specific miRNAs, which could be beneficial for patient care, particularly in cancer treatment. For targeting and eliminating miRNAs, some methods including Antisense Oligonucleotides

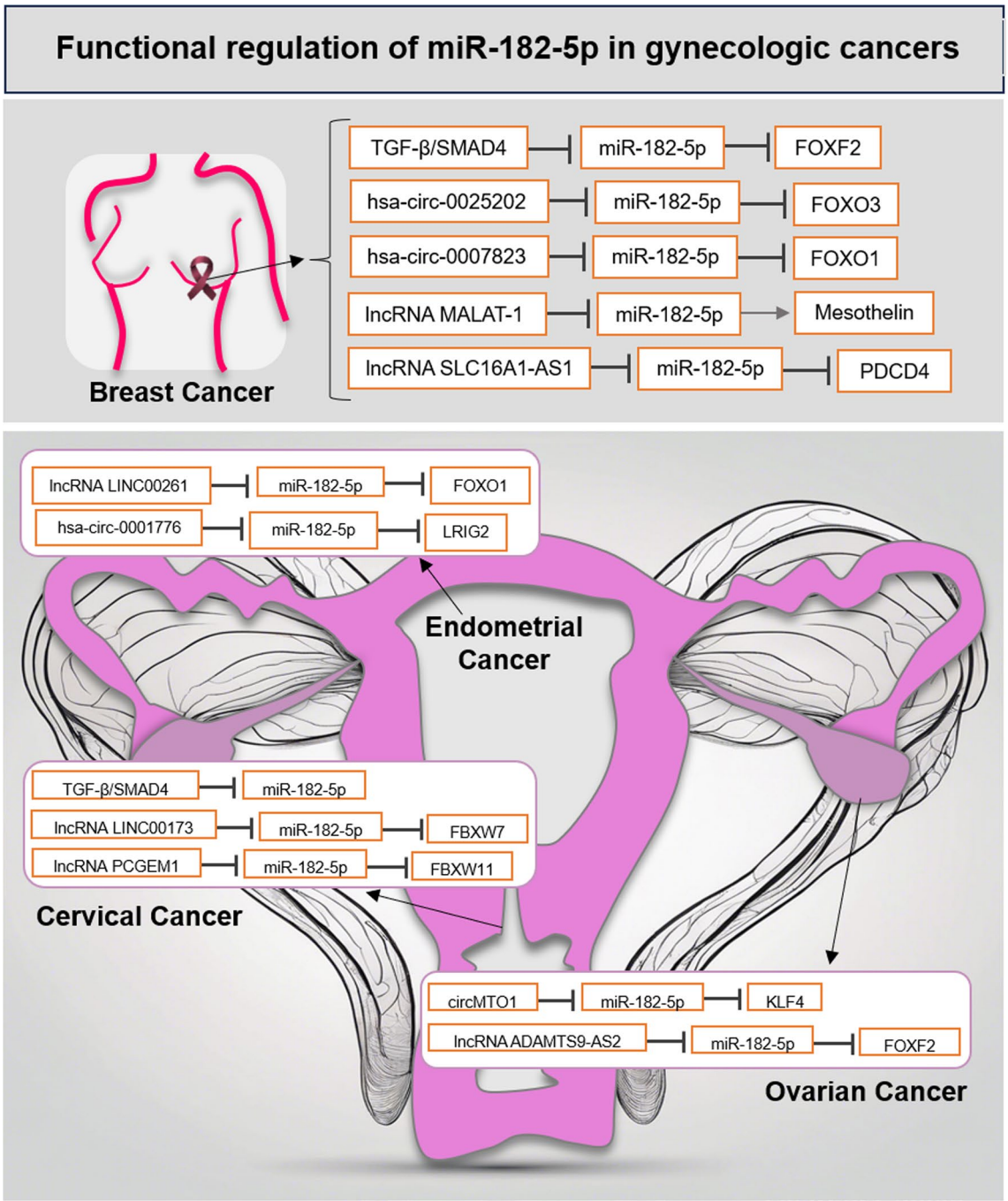

Fig. 2 Various ncRNAs and transcription factors can influence the expression of miR-182-5p in gynecologic cancer cells. Long ncRNAs and circular RNAs by directly targeting miR-182-5p can reduce its function. Besides, transcription factors by binding to the promoter region of the miR-182 gene activate or repress its transcription. Understanding the mechanisms governing this important miRNA may provide valuable insights for the development of targeted therapies

(ASOs) (chemically modified oligonucleotides) [116], miRNA sponges (some constructs with multiple binding sites for a specific miRNA) [117], Short Tandem Target (STR) (mimic the natural target sites of miRNAs) [118], CRISPR/Cas Systems (engineered to specifically target and degrade mature miRNA sequences) [119], and Decoy RNAs (synthetic RNA molecules) are commonly used [120]. The elimination or inhibition of specific miRNAs has significant potential in treating various diseases, particularly cancers where certain miRNAs play key roles in tumor progression and metastasis. By restoring normal gene expression patterns through these targeting strategies, it may be possible

Table 1 Functional regulation of miR-182 in gynecologic malignancies and the associated biologic consequences

Cancer type	Upstream molecule pathway	Regulation type	Outcome	References
Ovarian cancer	circMTO1	miR-182-5p repression	KLF15 overexpression; tumor growth suppression	[121]
	lncRNA ADAMTS9-AS2	miR-182-5p repression	FOXF2 upregulation; tumor suppression	[82]
Breast cancer	TGF-β/SMAD4	miR-182-5p overexpression	FOXF2 repression; increased metastatic potential	[56]
	hsa-circ-0025202	miR-182-5p repression	FOXO3a upregulation; reduced colony formation, migration and tamoxifen resistance	[57]
	hsa-circ-0007823	miR-182-5p repression	FOXO1 upregulation; Reduced TNBC cell viability and migration as well as apoptosis induction	[122]
	lncRNA MALAT-1	miR-182 repression	Decreased mesothelin expression; TNBC growth suppression	[123]
	lncRNA SLC16A1-AS1	miR-182 repression	PDCD4 upregulation; TNBC cell cycle arrest	[61]
Cervical cancer	TGF-β/SMAD4	miR-182 overexpression	Enhanced tumorigenesis	[94]
	lncRNA LINC00173	miR-182-5p repression	FBXW7 upregulation; reduced tumor cell proliferation and invasion	[124]
	lncRNA PCGEM1	miR-182 repression	FBXW11 upregulation; increased tumor proliferation and invasion	[125]
Endometrial cancer	lncRNA LINC00261	miR-182 repression	FOXO1 upregulation; suppressed tumor proliferation and invasion	[109]
	hsa-circ-0001776	miR-182 repression	LRIG2 upregulation; attenuated proliferation and glycolysis and increased apoptosis	[126]

Table 2 Biologic impressions by which miR-182 or a specific related subfamily functions as tumor-suppressive miRNAs in gynecologic cancers

Cancer type	miRNA	Target	Outcome	References
Ovarian cancer	miR-182	DDR2	Earlier FIGO stage and residual disease, extended patient survival	[127]
	miR-182-5p	CDK6	Increased cisplatin sensitivity	[128]
	miR-182	Mediator(s) which regulate caspase-mediated apoptosis	Enhanced OC cell apoptosis	[87]
Breast cancer	miR-182	MET	PI3K/AKT/mTOR pathway suppression and increased trastuzumab sensitivity	[62]
	miR-182-3p	TRF2	Reduced tumor growth, increased DNA damage and TNBC cell apoptosis	[63]
Cervical cancer	miR-182	DNMT3a	Elevated level of apoptosis and cell death	[98]
	miR-182	FBXW11	Deactivated NF-κB and β-catenin/TCF signaling, decreased CC cell proliferation and invasion	[125]
Endometriosis	miR-182	RELA	Deactivated NF-κB pathway, reduced proliferation, invasion, migration and EMT capability	[108]

OC ovarian cancer, *TNBC* triple-negative breast cancer, *CC* cervical cancer, *EMT* epithelial-to-mesenchymal transition

to improve patient outcomes and develop more effective therapies.

Conclusion

The emerging biologic and clinical implications of miR-182-5p in GCs highlight its significant role in the development and progression of these malignancies. miR-182-5p, belonging to the miR-183/96/182 cluster, regulates multiple target genes and signaling pathways, exerting a dual role in different types of tumors. Its dysregulated expression is associated with aberrant cell differentiation, immune system dysfunction, angiogenesis, EMT, and other cancer-related processes. The canonical pathway of miRNA biogenesis plays a crucial role in the generation of mature miR-182, with the microprocessor complex, DICER1, and the miRISC complex being key players in this process. Through sequence-specific binding, miR-182-loaded miRISC mediates gene suppression by mRNA degradation and translational blocking, further influencing cancer-related pathways. Given the prevalence

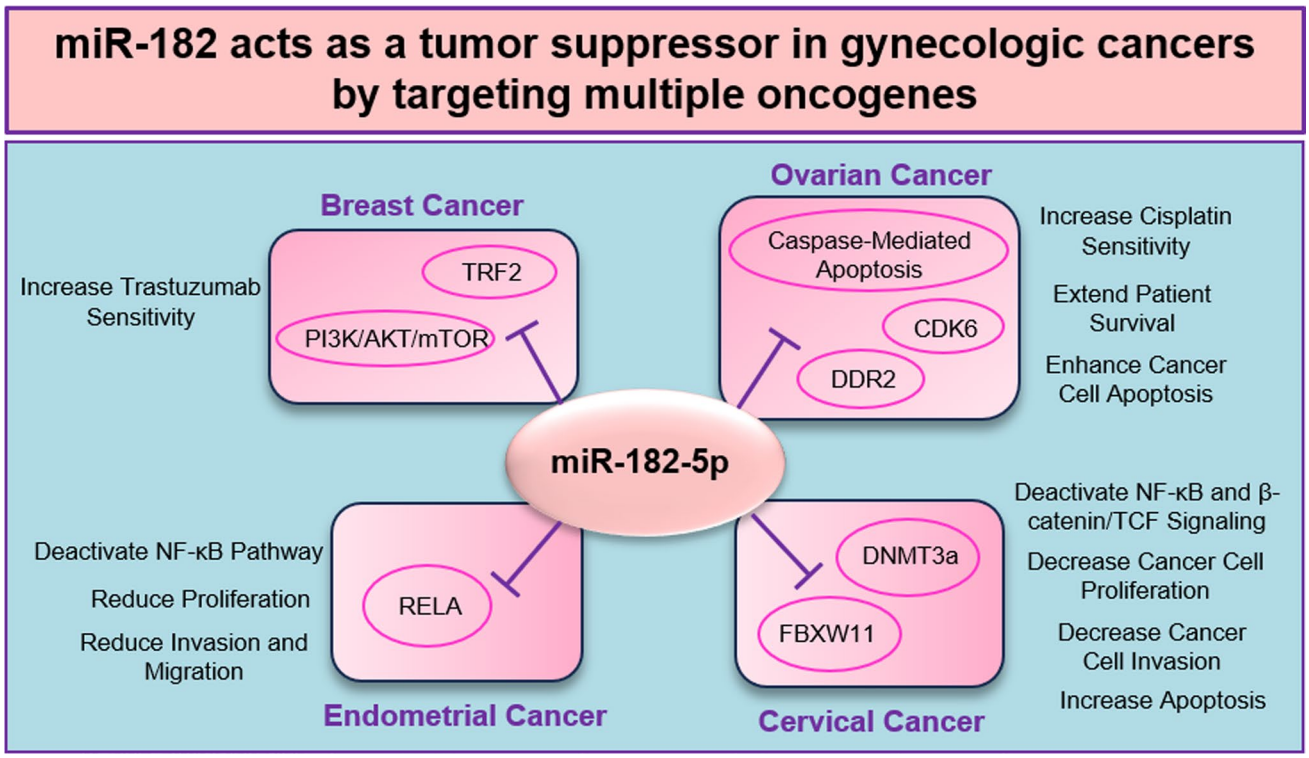

Fig. 3 The antitumor impacts of miR-182 in gynecologic cancers. miR-182 has been extensively studied for its role in the suppression of tumor cells. Emerging evidence suggests that mir-182 exerts significant antitumor effects in gynecologic cancers, through inhibition of cell proliferation, reduction of cell invasion and migration, induction of apoptosis, and inhibition of tumor growth and metastasis

of GCs among women and the challenges in their diagnosis, understanding the role of miR-182 in these malignancies holds great promise. It has the potential to serve as a diagnostic and prognostic marker, aiding in the timely detection and management of GCs. Further research into the specific mechanisms and downstream targets of miR-182-5p in GCs is warranted to unlock its full therapeutic potential and explore its utility in personalized treatment strategies.

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Declarations

Conflict of interest The authors declare no conflict of interest.

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

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