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REVIEW

Small non-coding RNAs as diagnostic, prognostic and predictive biomarkers of gynecological cancers: an update

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ABSTRACT

Introduction: Non-coding RNAs (ncRNAs) comprise a heterogeneous cluster of RNA molecules. Emerging evidence suggests their involvement in various aspects of tumorigenesis, particularly in gynecological malignancies. Notably, ncRNAs have been implicated as mediators within tumor signaling pathways, exerting their influence through interactions with RNA or proteins. These findings further highlight the hypothesis that ncRNAs constitute therapeutic targets and point out their clinical potential as stratification biomarkers.

Areas Covered: The review outlines the use of small ncRNAs, including miRNAs, tRNA-derived small RNAs, PIWI-interacting RNAs and circular RNAs, for diagnostic, prognostic, and predictive purposes in gynecological cancers. It aims to increase our knowledge of their functions in tumor biology and their translation into clinical practice.

Expert Opinion: By leveraging interdisciplinary collaborations, scientists can decipher the riddle of small ncRNA biomarkers as diagnostic, prognostic and predictive biomarkers of gynecological tumors. Integrating small ncRNA-based assays into clinical practice will allow clinicians to provide cure plans for each patient, reducing the likelihood of adverse responses. Nevertheless, addressing challenges such as standardizing experimental methodologies and refining diagnostic assays is imperative for advancing small ncRNA research in gynecological cancer.

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Small non-coding-rna; gynecological cancer; miRNAs (miRNAs); P-Element induced wimpy testis interacting (PIWI) RNAs (piRNAs); tRNA derived fragment (tRFs); ovarian cancer; endometrial cancer; cervical cancer

1. Introduction

One of the leading causes of mortality among women worldwide is gynecological malignancies, which encompass cancers of the cervix, ovary, uterus, vulva, and vagina [1]. The most prevalent types of these malignancies are endometrial, ovarian, and cervical cancers [2]. Despite the already implemented research, the molecular mechanisms underlying the development and pathophysiology of gynecological cancers remain unclear [3,4]. These diseases are complex and heterogeneous [5]. Therefore, early detection, precise diagnosis as well as novel targeted therapies are essential for improving patient survival rates and quality of life.

Recently, small non-coding RNAs (sncRNAs) have garnered noteworthy interest from researchers in gynecological oncology as potential biomarkers [6,7]. Cancer research studies have primarily focused on protein targets encoded by approximately 1% of the human genome [8]. However, the remaining 99% of the genome, which includes non-coding RNAs (ncRNAs), remains significantly unexplored [9]. Non-coding RNAs are categorized into two classes: sncRNAs, which are less than 200 nt in length (e.g. miRNAs, piRNAs, and tRFs), and long non-coding RNAs (lncRNAs) that are more than 200 nt in length (e.g. lincRNAs) [10–13] (Figure 1). In the context of gynecological malignancies, the discovery of numerous ncRNAs with structural or regulatory roles [14] has had a substantial impact on genetics, physiology, pathophysiology, and disease management. [15].

Furthermore, RNAs can serve as biomarkers for prognostic and diagnostic purposes in cancer, thereby influencing treatment decisions [16]. This approach allows for the simultaneous tailoring of treatment plans for individual patients [17]. In this review, we provide an updated overview of the significance of sncRNAs in gynecological cancers, emphasizing their roles as prognostic, predictive, and diagnostic biomarkers. Our objective is to identify specific clinical scenarios where the real-time application of sncRNAs as biomarkers could directly impact patient outcomes.

2. Gynecological malignancies

Gynecological cancer involves malignancies affecting the female reproductive tract [18]. The most common gynecological malignancy is endometrial cancer. This cancer type is characterized by new cases of 65,570 and deaths of 12,940 within a year in the United States of America. Of note, the 5-year relative survival rate of endometrial cancer is 95% for the localized disease [19]. Furthermore, cervical cancer affects approximately 14,480 women newly and 4,290 die of the disease every year, while the 5-year relative survival rate of patients with localized cervical cancer is 92% [20]. Another gynecological malignancy, ovarian cancer, while not as frequent as the previous one, is highly deadly, with 19,710 new cases and 13,270 deaths yearly, with the overall 5-year relative

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Article highlights

- Gynecological cancers, including ovarian, endometrial, and cervical cancers, are among the leading causes of mortality in women worldwide.
- Small non-coding RNAs (sncRNAs) like miRNAs, tRFs, and piRNAs hold significant potential as diagnostic and prognostic biomarkers in gynecological cancers.
- Many miRNAs are aberrantly expressed gynecological malignancies, demonstrating oncogenic or tumor suppressor roles.
- tRFs have emerged as novel regulators of gene expression in gynecological cancers, influencing critical pathways like PI3K/AKT/mTOR and Wnt/β-catenin.
- piRNAs regulate gene expression through post-transcriptional mechanisms and DNA methylation.
- circRNAs act as miRNA sponges, influencing oncogenes that regulate cell proliferation and invasion.

survival rate of 93% for those diagnosed at an early stage [21]. The lowest incidence rate is registered with vaginal cancer, with 1,410 new cases and 430 deaths annually; the 5-year relative survival for localized diseases is 81% [22]. Undoubtably, these statistics reveal the importance of the detection and treatment of diseases at an early stage for enhanced patient outcomes.

Primary surgical intervention generally constitutes the initial treatment approach and is most effective across various tumor types when the disease is diagnosed at an early stage. Recent advancements in therapeutic strategies have significantly improved the early detection of endometrial and cervical cancers. However, ovarian cancer frequently presents at an advanced stage, making curative treatment challenging [23].

2.1. Endometrial cancer

Endometrial cancer represents the most prevalent gynecological malignancy in many nations worldwide [24]. Risk factors include obesity, hormone replacement therapy, tamoxifen use, diabetes, and genetic conditions, such as Lynch syndrome [24]. Among the common manifestations, atypical vaginal bleeding, particularly postmenopausal or irregular menstrual bleeding should be mentioned. Endometrial malignancy often leads to abnormal uterine bleeding, which, in some cases, serves as an early indicator of the disease [25]. However, recovery likelihood varies significantly based on factors, such as tumor type, histological subtype, and stage at diagnosis. The molecular biology of endometrial cancer is highly complex, involving pathways, including PI3K/AKT/mTOR, Wnt/β-catenin, and hormonal signaling that involves estrogen and progesterone [26]. Additionally, genetic alterations, including point mutations in genes like *PTEN* and *TP53*, along with epigenetic aberrations, have been confirmed to contribute to endometrial carcinoma [27].

Recent discoveries regarding the roles of ncRNAs, including miRNAs and lncRNAs, in the progression of endometrial cancer highlight the need for a deeper understanding of their contributions to these diseases [28]. Indicatively, they have been found to influence the phosphorylation states of signaling cascades, protein stability, and degradation [29]. Identifying the genetic background of uterine cancer and the clinical significance of ncRNAs has crucial medical implications [30]. Understanding these factors will facilitate accurate diagnosis, risk factor determination, and the identification of treatment targets suitable for individual patients [31]. Significant progress has been made in research elucidating the complexity of sncRNAs and the biology of endometrial cancer. This

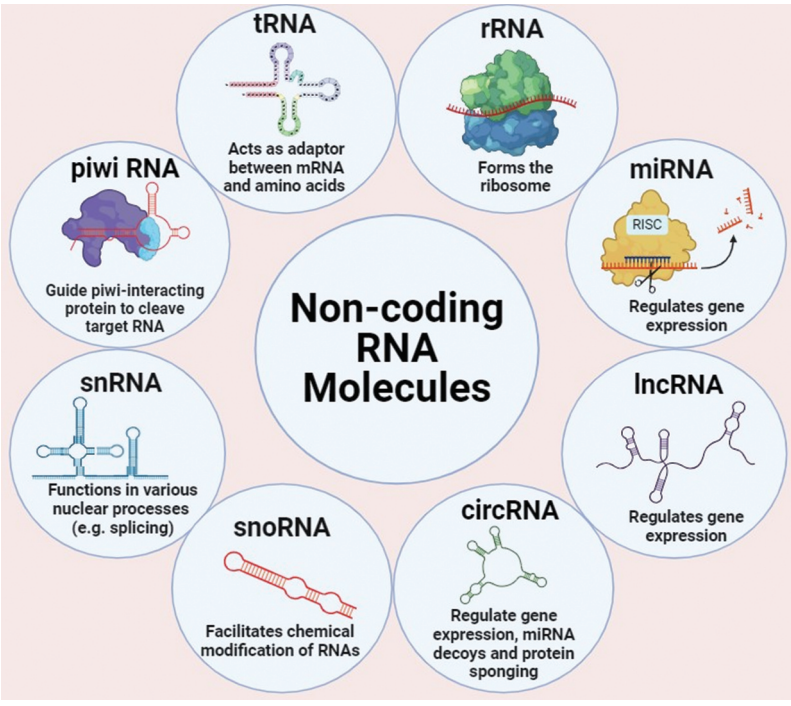

Figure 1. Types of non-coding RNA molecules.

section aims to provide essential knowledge about the molecular landscape of endometrial cancer and the potential of sncRNAs to improve patient outcomes [32].

2.2. Cervical cancer

Cervical cancer, originating from the cervix, the lower segment of the uterus, represents a significant health burden worldwide [33]. Its etiology is predominantly mediated by chronic infection with high-risk strains of human papillomavirus (HPV) [34], along with contributing factors such as smoking, immunodeficiency, early or multiple sexual encounters, and a prior history of sexually transmitted infections. Although initially asymptomatic, cervical cancer may present with vaginal bleeding or pelvic discomfort in advanced stages [35]. Screening methods, including HPV testing and the Pap test, aim to detect precancerous changes early. Standard treatment options include surgery, radiation therapy, chemotherapy as well as targeted therapies. However, effective prevention and early detection remain challenging in low-resource settings due to limited access to HPV vaccination and screening services. It is well-established that HPV has an oncogenic role, particularly strains HPV-16 and HPV-18 [36]. The viral oncoproteins E6 and E7 disrupt crucial tumor suppressor pathways involving p53 and pRb proteins, leading to uncontrolled cell proliferation and genomic instability [37].

In the pathophysiology of cervical cancer, the deregulation of sncRNAs, especially miRNAs, has been identified as a key factor [38]. This review explores the potential of these molecules as diagnostic and prognostic biomarkers for cervical cancer, highlighting their roles in critical pathways, such as epithelial-mesenchymal transition (EMT) and metastasis [39]. Additionally, their potential as predictive biomarkers for treatment responses and prognosis enhances their significance, demonstrating how oncologists can tailor personalized treatments for individual patients. Numerous studies have already highlighted the potential of sncRNA-mediated therapy, such as the use of miRNA mimics or inhibitors in targeted therapy and overcoming resistance in cervical cancer treatment [40]. This underscores the strong association between cervical cancers and sncRNAs as biomarkers in cancer therapy [41].

2.3. Ovarian cancer

Ovarian cancer is a severe clinical condition with limited treatment options [42]. Unfortunately, this type of malignancy is often detected at an advanced stage. Diagnostic protocols typically involve imaging techniques, such as ultrasound and CT scans, alongside serological biomarkers like CA-125 [43,44]. Treatment modalities include surgical intervention, chemotherapy, and targeted therapies [45]. Risk factors for ovarian cancer encompass genetic predispositions, such as mutations in *BRCA1* and *BRCA2* genes, advancing age, and a familial history of the disease [46]. Key genetic alterations in ovarian cancer include mutations in tumor-suppressor genes such as *TP53*, *BRCA1*, and *BRCA2*, amplification of *KRAS* and *BRAF* oncogenes as well as dysregulation of signaling pathways like Wnt/β-catenin, highlighting the multifaceted etiology of the disease [47].

Small non-coding RNAs (sncRNAs), including miRNAs, tRNA-derived small RNAs, and PIWI-interacting RNAs, play significant roles by modulating tumor pathways such as cell cycle progression, apoptosis, DNA repair, and drug resistance, thereby contributing to tumor aggressiveness and treatment outcomes [48]. Additionally, sncRNAs can serve as valuable biomarkers for treatment response and prognostication, providing critical insights into the efficacy of treatments and individual patient outcomes. This review offers a molecular perspective on epithelial ovarian cancer and underscores the impact of sncRNAs on the precision and effectiveness of ovarian cancer therapy [49].

3. Small non-coding RNAs (sncRNAs)

In cancer research, while traditional therapeutic targets have primarily focused on protein-coding genes, ncRNAs have emerged as crucial regulators of gene expression involved in cancer development and progression (Figure 1). It has recently been demonstrated that ncRNAs play significant roles in regulating genes associated with cancer initiation, metastasis, and treatment resistance [50]. These molecules control gene expression and cellular functions, making their dysregulation a critical feature of cancer. This dysregulation is linked to multiple oncogenic processes, including tumor development, metastasis, and resistance to therapy.

Non-coding RNAs, distinguished by their inability to produce proteins, can be classified into small (less than 200 nucleotides) or long (exceeding 200 nucleotides) variants based on their size or functional roles as housekeeping and regulatory RNAs [51]. The following section offers a brief overview of specific subclasses of sncRNAs, underlining the significance of comprehending these variations in our understanding of cancer biology.

The class of ncRNAs is characterized by the lack of protein-coding capacity and can be categorized based on their size into two major groups: sncRNAs (<200 nt) and lncRNAs (>200 nt). They can also be classified based on their functional roles as housekeeping and regulatory RNAs [51]. The following section provides an overview of specific subclasses of sncRNAs, emphasizing the importance of understanding their expression profiles and functional roles to enhance our comprehension of cancer biology.

3.1. microRNAs (miRNAs)

Undoubtably, microRNAs (miRNAs) is most extensively studied subclass of sncRNAs, representing 18–26 nt single-strand RNA molecules [52] that bind to the 3′ untranslated regions (UTR) of mRNAs, thereby regulating post-transcriptional gene expression by promoting mRNA degradation or inhibiting translation [52]. In gynecological cancers, perturbations in miRNA expression profiles have been found to contribute to neoplastic transformation, tumor progression, and metastasis [53]. For instance, ovarian cancer specific miRNAs, such as the miR-200 family members, are involved in regulating EMT, a critical process driving tumor invasion and metastasis [54].

Aberrant levels of miR-200 family members are associated with advanced stage disease, metastatic potential and poor prognosis in ovarian cancer patients [55]. Similarly, in cervical cancer, dysregulated expression of miR-21, miR-34a, and miR-375, have been linked to abnormal cell proliferation, migration, and invasion, highlighting their roles as diagnostic and prognostic biomarkers [55]. Therefore, understanding the complex regulatory networks of miRNAs in gynecological cancers facilitates the identification of new biomarkers and drug targets, advancing diagnostic and predictive tools for patient care and treatment [17].

3.1.1. miRNAs in gynecological cancers

Aberrant miRNA expression has been firmly associated with the development of various gynecological tumors, including ovarian, cervical, and endometrial cancers [56]. In general, miRNAs have been found to have oncogenic or tumor suppressor roles in multiple cancers (Table 1). In ovarian cancer, miRNAs such as the miR-200 family, miR-21, and miR-155 have been implicated in tumor aggressiveness, chemoresistance, and poor prognosis [57]. These miRNAs are potent regulators of critical pathways such as EMT, apoptosis evasion, and DNA repair, which are essential for cancer progression and metastasis [58]. Similarly, cervical and endometrial cancers also exhibit dysregulated miRNA expression profiles, highlighting their diagnostic utility and potential as therapeutic targets [59,60].

Insights into the functions of miRNAs in cancer biology promise the development of precision therapies and personalized treatment methods. By elucidating the multifaceted regulatory roles of miRNAs, researchers aim to identify novel biomarkers capable of predicting early cancer diagnosis, prognostic outcomes, and treatment responses in women with gynecological malignancies [61].

3.1.2. miRNAs in ovarian cancer pathogenesis

Ovarian cancer has been characterized by aberrant expression and functionality of multiple miRNAs, inducing tumorigenesis, progression, and metastasis [62]. Specific miRNAs exhibit tumor-suppressive functions in ovarian cancer by selectively targeting genes or oncogenes involved in cancer proliferation

Table 1. List of miRNAs with oncogenic and tumor suppressor roles in gynecological malignancies.

Type	miRNA	Function	Targets	Mechanism	Gynecological Malignancy
Oncogenic	miR-21	Promotes cell proliferation inhibits apoptosis	PTEN PDCD4	Downregulates tumor suppressors	Ovarian Cervical
	miR-9	Promotes cell migration invasion	E-cadherin NF-kB	Enhances oncogenic signaling	Ovarian
	miR-135b	Promotes cell proliferation & invasion	APC RECK	Downregulates tumor suppressor genes	Ovarian
	miR-31	Promotes cell proliferation, migration, invasion	LATS2 RhoA	Enhances oncogenic signaling	Cervical Ovarian
	miR-183	Promotes cell proliferation & migration	EGR1 PTEN	Downregulates tumor suppressors	Ovarian
	miR-24	Promotes cell proliferation inhibits apoptosis	MYC BCL2	Upregulates cell cycle and survival	Ovarian
	miR-155	Enhances inflammation, promotes cell growth	SHIP1 SOCS1	Modulates immune response	Ovarian
	miR-10b	Promotes metastasis	HOXD10 RhoC	Enhances cell migration and invasion	Ovarian
	miR-373	Promotes cell proliferation and invasion	CD44 LATS2	Enhances stem cell-like properties	Ovarian
	miR-221	Promotes cell cycle progression inhibits apoptosis	p27 p57	Downregulates cell cycle inhibitors	Ovarian
Tumor Suppressor	miR-34a	Induces cell cycle arrest promotes apoptosis	BCL2 CDK6	Upregulates pro-apoptotic proteins	Ovarian
	miR-145	Inhibits cell growth promotes differentiation	MYC FSCN1	Suppresses oncogenic transcription	Ovarian Cervical
	miR-200c	Inhibits EMT	ZEB1 ZEB2	Restores epithelial phenotype	Ovarian
	miR-214-3p	Inhibits cell proliferation promotes apoptosis	β-catenin PTEN	Downregulates Wnt/β-catenin signaling	Ovarian
	miR-141	Inhibits cell proliferation promotes apoptosis	ZEB1 ZEB2	Modulates EMT	Ovarian
	miR-152	Inhibits cell proliferation promotes apoptosis	DNMT1 MET	Downregulates DNA methylation	Ovarian
	miR-375	Inhibits cell proliferation promotes apoptosis	JAK2 PDK1	Downregulates survival pathways	Ovarian
	miR-34a-5p	Induces apoptosis inhibits cell cycle progression	BCL2 SIRT1	Upregulates pro-apoptotic pathways	Ovarian
	miR-424	Induces cell cycle arrest inhibits angiogenesis	VEGF CCND1	Suppresses angiogenic factors	Ovarian Cervical
	miR-6076	Induces apoptosis inhibits cell migration	Notch2 CDH1	Downregulates Notch signaling	Breast
	miR-135a	Inhibits cell proliferation & migration	JAK2 ROCK1	Downregulates JAK/STAT signaling	Ovarian
	miR-1271	Inhibits cell proliferation induces apoptosis	BCL2 Notch1	Downregulates Notch signaling	Ovarian
	miR-100	Inhibits cell proliferation promotes apoptosis	mTOR IGF1R	Downregulates mTOR signaling	Ovarian
	miR-513	Inhibits cell proliferation promotes apoptosis	PLK1 Bcl-2	Downregulates survival pathways	Cervical

and dissemination [63]. Notably, miR-34, miR-200 and let-7 family members represent major examples of miRNAs with tumor-suppressive functions [51]. Reduced levels of these miRNAs in tumor tissues often result in the upregulation of their target genes, such as *CCND1*, *MYC*, and *ZEB1* [64]. While several miRNAs act as tumor suppressors by targeting oncogenes or genes that counterbalance tumor activity, others promote tumorigenesis by downregulating tumor suppressor genes [65]. For instance, miR-21, miR-155, and miR-214 are upregulated in ovarian cancer and promote tumor growth, invasion, and chemoresistance by targeting *PTEN* and *TP53*, respectively [66].

Chemoresistance constitutes a significant challenge in the treatment of ovarian cancer, with increasing evidence supporting that miRNAs are critical mediators of chemotherapy drug resistance [67]. Specific miRNAs, such as miR-200c and miR-214, contribute to the development of chemoresistance by suppressing apoptosis and regulating genes involved in drug efflux mechanisms [67]. Understanding how miRNAs influence the development of ovarian cancer is clinically important. Targeting dysregulated miRNAs or their downstream signaling pathways presents a promising approach for developing novel therapeutics [68]. Strategies are based on miRNA mimics to restore the function of tumor-suppressor miRNAs and miRNA inhibitors (anti-miRNAs) to block the activity of oncogenic miRNAs [69]. Additionally, miRNAs serve as biomarkers for prognosis and therapy response in ovarian cancer patients, facilitating the development of personalized healthcare. These scientific findings enhance our understanding of the molecular mechanisms driving tumor growth and pave the way for specialized therapies [70].

3.1.3. miRNAs in endometrial cancer pathogenesis

It is now known that miRNA expression affects endometrial cancer prognoses, such as lymph node metastases, lymphovascular space invasion, overall survival, and recurrence-free survival [71]. More importantly, miRNAs are differentially expressed between normal endometrial tissue and endometrial cancer [72]. Indicatively, miR-99b, miR-143, miR-145, miR-193b and miR-204 are included in the confirmed catalog of downregulated miRNAs, while miR-9, miR-92a, miR-141, miR-182, miR-183, miR-186, miR-200a, miR-205a, miR-222, miR-223, miR-410, miR-429, and miR-1228 have emerged as upregulated miRNAs [73]. In addition, research findings have highlighted that miRNA expression profiles are associated with stage, grade, relapse, and nodal metastases in endometrial cancer, whereas numerous miRNAs control endometrial cancer cell proliferation by silencing their target genes [74].

Specific miRNAs function as tumor suppressors in endometrial cancer by targeting oncogenes or genes implicated in cancer development and progression. For instance, miR-200 family members, including miR-34a and miR-152, are frequently downregulated in endometrial cancer tissues. These miRNAs inhibit cell proliferation, migration, and invasion by targeting genes such as *ZEB1*, *CCND1*, and *BCL-2* [71]. Conversely, other miRNAs exhibit oncogenic properties in endometrial cancer by targeting tumor suppressor genes or genes that suppress tumorigenesis. The overexpression of miR-21, miR-182, and miR-205 promotes cancer progression, invasion, and metastasis by targeting genes such as *PTEN*, *TIMP3*, and *CDH1* [64]. Furthermore, miRNAs can alter the expression of hormone receptors (ER, PR) and disrupt associated signaling pathways, influencing cell proliferation and differentiation in response to hormonal stimuli [75].

Finally, one important mechanism in cancer metastasis is the EMT. Epithelial cells do change into a mesenchymal-like shape with invasive properties during EMT. EMT's fine-tuning of cancer processes is greatly mediated by miRNAs [76]. Therefore, understanding the role of miRNA as a strong promoter of endometrial cancer pathogenesis reveals the most crucial molecular mechanisms of tumor carcinogenesis. This knowledge enables the application of personalized methods and specific medicines to achieve better outcomes for endometrial cancer patients [77].

3.1.4. Role of miRNAs in cervical cancer pathogenesis

Cervical cancer typically arises from prolonged infection with high-risk human papillomavirus (HPV), specifically HPV types 16 and 18 [34]. Numerous microRNAs (miRNAs) function as tumor suppressors by negatively regulating genes that encode oncogenic or tumorigenic proteins. It has been observed that the miR-34 family, miR-143, and miR-375 are downregulated when comparing adjacent normal tissues to cancerous tissues [78]. Studies have confirmed that miRNAs act as critical mediators in the repression of gene expression, targeting oncogenes like *MYC*, *RAS* and matrix metalloproteinases (*MMPs*). Through suppression, they restrain tumor cell proliferation, migration, and invasion [34]. Besides their tumor suppressor roles, several miRNAs (e.g. miR-21) exhibit dual functions by downregulating genes that inhibit tumors [79]. Conversely, miR-155 and miR-214 demonstrate oncogenic effects in cervical cancer by targeting the tumor suppressor genes *TP53* and *PTEN* [80,81].

HPV infection induces reprogramming of the miRNA profile in cervical cancer cells at various stages, impacting viral replication, immune responses as well as tumor progression [82]. Specific miRNAs (e.g. miR-375 and miR-218) are directly targeted by HPV major proteins E6 and E7, leading to their aberrant expression and contributing to cervical cancer progression [83]. Of note, miRNAs play a pivotal role in regulating EMT-related signaling pathways in cancer cells, which constitute critical pathways for metastasis. For instance, the miR-200 family members suppress EMT by targeting *ZEB1*, *ZEB2*, and *CDH1*, thereby maintaining epithelial morphology and inhibiting cancer invasion into the bloodstream [84]. Understanding the role of miRNAs in the etiology of cervical cancer can lead to more effective treatment options [85].

3.2. tRNA-derived fragments (tRFs)

The class of tRNA-derived fragments (tRFs) comprises sncRNA molecules produced through specific cleavage events of tRNA transcripts [86]. Based on their length and origin from either primary or mature tRNA, tRFs are categorized into various types. Among these, stress-induced tRFs, commonly referred to as tRNA halves (tiRNAs, tiRs, or tRHs), are generated by specific cleavage of mature tRNAs within their anticodon loop by angiogenin, resulting in fragments typically ranging

from 31 to 40 nucleotides in length [87]. tRFs originate from mature tRNAs and are classified based on the location of the incisions in four groups: tRF-1, tRF-3, tRF-5, and i-tRF (tRF-2). Briefly, tRF-5 consists of fragments derived from the 5′ end of mature tRNAs (14–30 nt), while tRF-3 is produced from the 3′ end of mature tRNAs (18–22 nt) [88]. Similarly, i-tRF (or tRF-2), is produced from endonucleolytic cleavages within the internal structure of mature tRNA, excluding both the 5′and 3′ ends [89]. Studies have demonstrated that tRFs exhibit unique biological roles in malignancies and stress-induced diseases [90]. Some tRFs bind to cytochrome c or promote virus replication to prevent cell death [91]. Consequently, tRFs may emerge as novel therapeutic targets for disease management [92]. In summary, tRFs represent a diverse class of sncRNAs with multifaceted functions and significant potential implications for human health and disease.

3.2.1. tRFs in gynecological cancers

Recent clinical research and experimental models have indicated that specific tRFs (e.g. tRF-03357 and tRF-03358) may serve as novel regulators of gene expression by either substituting the translation initiation complex eIF4G/eIF4E on the mRNA cap or by controlling mRNA stability in gynecological malignancies (Figure 2) [93,94]. Specifically, several tRF-3 fragments have been found downregulated in cancerous tissues compared to normal ovarian tissues, correlating with clinicopathological variables and patient survival outcomes [95]. Additionally, tRFs are implicated in both PI3K/AKT/mTOR and Wnt/β-catenin pathways, which are essential for ovarian cancer pathogenesis [96].

Additionally, tRFs play significant roles in cellular processes like cell proliferation, apoptosis, and invasion in ovarian cancer cells [86,97]. Similarly, aberrant expression of tRFs has been firmly linked to the pathogenesis of endometrial cancer, contributing to tumor initiation, progression, and metastasis. For instance, tRF-5, derived from specific tRNA fragments, shows elevated expression levels in endometrial cancer tissues compared to normal endometrial tissues, with expression levels positively correlating with cancer severity and stage [16].

Functional studies have demonstrated that tRFs influence critical processes in endometrial cancer pathogenesis, including the PI3K/AKT/mTOR and estrogen signaling pathways [98,99]. Moreover, tRFs have been associated with tumor proliferation and migration in cervical cancer [100]. Recent findings suggest that tRFs are overexpressed in cervical cancer tissues compared to healthy cells [101,102]. Indicatively, tRF-1001 is derived from the 3′ end of a Ser-TGA tRNA precursor transcript that is not retained in the mature tRNA and is highly expressed in a wide range of cancer cell lines, including cells originating from gynecological cancers. Studies have shown that its expression is linked to the regulation of cell cycle genes, particularly those involved in the G2/M transition [103]. Additionally, tRF and tiRNA microarray investigation studies revealed that tRF-Glu49 possesses a potential tumor suppressor function in cervical carcinoma. RT-qPCR assays highlighted that tRF-Glu49 was downregulated in cervical carcinoma tissues, while analysis of the clinicopathological data supported that it is associated with less aggressive clinical features and improved prognosis [104]. At the mechanistic level, tRF-Glu49 regulates the fibrinogen-like protein-1 (FGL1) oncogene, modulating cervical cell proliferation, migration, and invasion processes. Another important case of tRF in gynecological cancers corresponds to the exosomal tRF-20-S998LO9D in endometrial carcinoma. Overexpression of tRF-20-S998LO9D inhibited proliferation, migration and invasion and promoted apoptosis in endometrial carcinoma cells, whereas functional studies revealed that it has a tumor

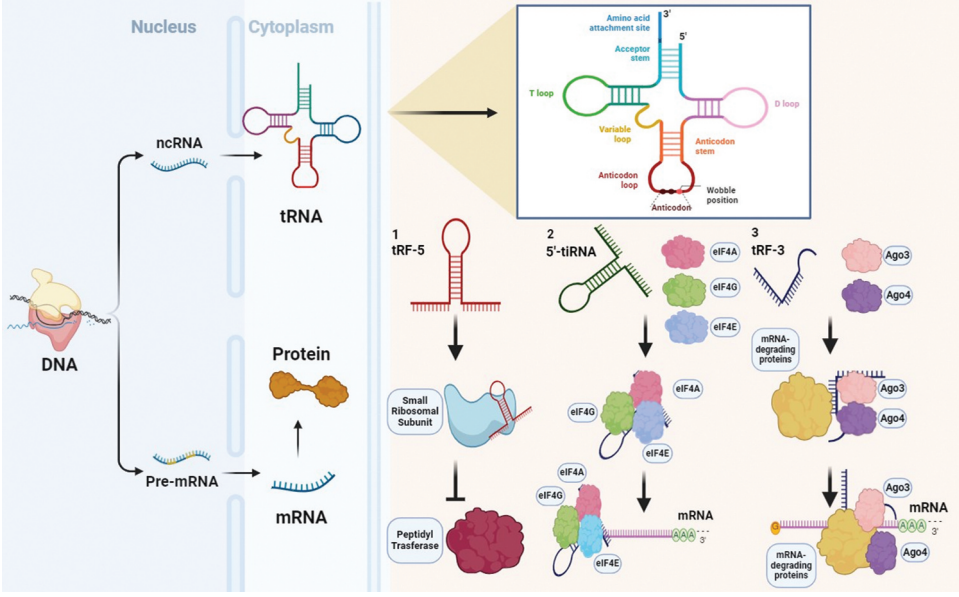

Figure 2. Gene regulation mediated by tRF and tiRNA: (1,2) Translation inhibition: target gene protein abundance is decreased when tRF binds to small ribosomal subunits and limits peptidyl transferase activity. By substituting the translation initiation complex elf4g/eif4e on the mRNA cap with an RNA G-quadruplex (RG4s), 5′ tiRNA suppresses translation. (3) Controlling mRNA stability: mRNA-degrading enzymes can destroy the target mRNA when tRF-3, argonaute 3 (Ago3), and Ago4 bind to mRNA. tRFs work similarly to miRNAs in suppressing the expression of genes linked to cancer. An RNA-induced silencing complex (RISC) is formed when binding proteins such as argonaute (ago) protein and others to the 3′ untranslated region (3′UTR) of the target mRNA.

suppressor effect by upregulating SESN2 protein levels [105]. Interestingly, a recent study in high-grade serous ovarian cancer revealed that a total of 27 tRFs were differentially expressed between tumor and control samples. More specifically, RT-qPCR findings highlighted that tRF-03357 and tRF-03358 were significantly upregulated in tumor samples as compared to the controls, suggesting a tumor biomarker role in this type of malignancy [95]. Furthermore, functional studies revealed that tRF-03357 promotes cell proliferation, migration and invasion in SK-OV-3 cells, further enhancing the notion that tRFs have significant roles in carcinogenesis and cancer progression.

3.3. Piwi-interacting RNAs (piRNAs)

A subclass of sncRNAs, typically ranging from 24 to 31 nucleotides in length, is known as PIWI-interacting RNAs (piRNAs). These sncRNAs lack unique secondary structural patterns and exhibit a notable preference for a tenth-position adenosine or a 5′-terminal uridine. They execute their regulatory roles by interacting with nuclear RNA-binding proteins called PIWI proteins, which are critical for their biological activity [106]. The group of piRNAs were first identified in the testes of Drosophila melanogaster, where they were recognized as a unique class of 'long siRNAs' essential for the silencing of the X chromosome [107]. Based on their source, piRNAs can be discriminated into three major groups: transposon-derived, mRNA-derived and lncRNA-derived piRNAs [108]. Transposon-derived piRNAs produce both antisense and sense piRNAs when transcribed from both genomic strands. LncRNA-derived piRNAs originate from the entire transcript, while mRNA-derived piRNAs are typically produced from 3′ untranslated regions (UTRs). Notably, Dicer, an enzyme crucial in RNA interference pathways, is generally not involved in processing these precursor molecules, which arise from specific genomic loci containing repetitive sequences [108]. Post-transcriptional modifications are essential for piRNA maturation, with mature piRNAs having 3′ termini modified by 2′-O-methylation. Instead of guiding AGO-clade proteins involved in miRNA and siRNA pathways, piRNAs direct PIWI-clade argonaute proteins (PIWI proteins) [109].

PIWI/piRNAs enhance the expression of target genes via post-transcriptional regulation mechanisms, including the recruitment of histone methyltransferases (HMTs) and heterochromatin protein 1 (HP1) [110]. Through a process mediated by DNA methylation, piRNAs achieve H3K9 methylation, resulting in the epigenetic silencing of transposons (Figure 3). Additionally, piRNAs regulate protein stability and control mRNA levels by complementary binding to their 3′UTR regions [111]. For instance, piRNA-54265 interacts with the PIWIL2 protein, forming the PIWIL2/STAT3/phosphorylated-SRC (p-SRC) complex, which activates STAT3 signaling. This signaling pathway promotes cell growth, metastasis, and chemoresistance in colorectal cancer cells [112]. Recent studies have shown that PIWI protein expression, particularly PIWIL1, PIWIL2, PIWIL3, and PIWIL4, is reactivated in various malignancies [113]. The association of PIWI proteins with critical cancer characteristics such as rapid cell division, evasion of apoptosis, genetic instability, high invasive activity, and metastasis suggests that they play a crucial role in cancer [110]. The expression of piRNAs/PIWI proteins in non-germline tumors is consistent with the expression of germline genes and cancer, indicating abnormal expression of germline-specific genes in non-germline malignancies [114].

3.3.1. Piwi-interacting RNAs in gynecological cancers

Growing functional data indicates that piRNAs are crucial in coordinating epigenetic modifications associated with carcinogenesis and in regulating post-transcriptional mRNA and protein stability [115]. Notably, the PIWI – piRNA complex promotes a stem-like state in cancer cells, or cancer stem cells (CSCs), driving cancer formation and progression [116]. These CSCs often arise from cells undergoing EMTs, gaining the capacity to spread [117]. This capability is facilitated by epigenetic alterations that allow adaptability to the tumor microenvironment [118]. Such changes include global DNA hypomethylation, histone hypoacetylation, and site-specific DNA hypermethylation. These modifications result in the activation of oncogenes like

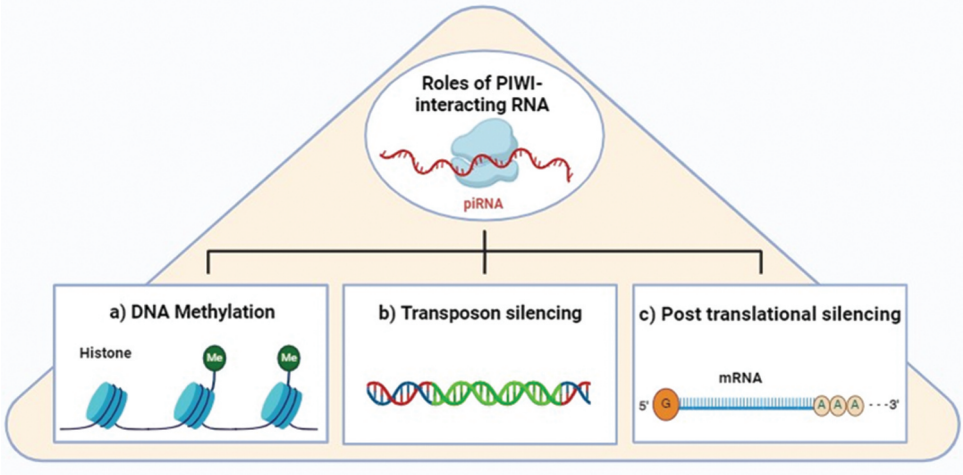

Figure 3. Piwi-interacting RNAs (piRNAs) are crucial for a variety of gene silencing strategies, such as DNA methylation, transposon silencing, post-translational silencing and histone modification.

CCND2 and *RRAS* and the silencing of tumor suppressor genes, such as *RB1* and *CDKN2A* [119].

Interestingly, dysregulated piRNA expression in cancer tissues is associated with localized DNA hypermethylation and global hypomethylation, potentially identifying unique cancer epigenetic characteristics [120]. Analyses of gynecologic cancers have elucidated the exploratory nature of piRNA molecules and their clinical implications. For instance, in ovarian cancer, distinct subtypes, such as endometrioid, have been differentiated based on piRNA expression profiles between normal ovaries and cancerous tissues [121]. Specific piRNAs target various mRNA transcripts involved in promoting cancer and exhibit diverse expression patterns, such as piR-52207 and piR-33733 [122]. These piRNAs are involved in tumorigenicity and cancer progression through the regulation of the post-transcriptional process. Regarding gynecological malignancies, research findings have confirmed that piR-52207 targets mRNA transcripts of 10 genes (*S100PBP*, *ZMYM6*, *MTR*, *FAM114A1*, *WAC*, *NUDT4*, *MPHOSPH8*, *ACTR10*, *JOSD1*, *EIF2S3*) in endometrioid ovarian cancer, whereas both piR-52207 and piR-33733 target 7 genes (*ACTR10*, *C2CD2*, *LIAS*, *MPHOSPH8*, *PLEKHA5*, *TMEM159*, *TMX4*) in serous ovarian cancer [119]. Consequently, major signal transduction pathways like PI3K/AKT, Wnt/β-catenin and MAPK/ERK are affected, leading to the deregulation of cell cycle proliferation and metastasis [123,124]. Therefore, both overexpression and downregulation of the mentioned piRNAs could represent putative indicators of cancer outcome and future treatment methods.

3.4. Circular RNAs (circRNAs)

Circular RNAs (circRNAs) represent a unique class of ncRNAs characterized by their covalently closed loop structure, which makes them resistant to exonucleases and thus more stable than linear RNAs [125]. They are produced through a back-splicing process where a downstream splice donor is joined to an upstream splice acceptor. CircRNAs have been found to play significant roles in gene regulation by acting as microRNA sponges, interacting with RNA-binding proteins, and potentially being translated into proteins [125]. Their expression is often tissue-specific and developmentally regulated, suggesting their involvement in various biological processes and diseases. Recent research has implicated circRNAs in cancer, neurodegenerative diseases, and cardiovascular disorders, highlighting their potential as biomarkers and therapeutic targets [126,127]. Despite the growing understanding of circRNAs, challenges remain in elucidating their comprehensive functions and mechanisms of action in different cellular contexts.

3.4.1. circRNAs in gynecological cancers

Research findings have confirmed the important role of circRNAs in the regulation of several gynecological malignancies to different extents and mechanisms [128]. Specific circRNAs related to ovarian cancer (e.g. circHIPK3, circMTO1, and circ-ITCH) were proven to sponge miRNAs (e.g. miR-124 and miR-145) and thus affect oncogenes regulating cell proliferation and invasion [129]. In cervical cancer, circEIF4G2 has been found to interact with miR-218, promoting cell proliferation and migration via the miR-218/HOXA1 pathway [130]. Similarly, in endometrial cancer, it has been reported that Circ_PUM1 is capable of binding to miR-136 and up-regulating its target gene NOTCH3, hence promoting the development of endometrial cancer [131]. The mentioned circRNAs present different expression profiles that are related to cancer development; thus, they could be exploited as tumor biomarkers for prediction and early detection. Last but not least, it is necessary to determine their exact functions and effectiveness in gynecological malignancies to develop effective approaches to the disease and enhance patients' prognosis.

3.5. sncRNAs and therapeutic approaches

Efforts to target sncRNAs in gynecological malignancies have led to the development of techniques aimed at manipulating their expression or function to control disease progression. Antisense oligonucleotides (ASOs) are employed to antagonize, deactivate, or degrade siRNAs and other sncRNAs, such as miRNAs [132]. This helps inhibit the growth of cancer by reducing the activity of oncogenic miRNAs. Conversely, mimics can be used to enhance the levels and activity of tumor-suppressive miRNAs, while antagomiRs can inhibit oncogenic miRNAs [133]. Additionally, small-molecule inhibitors can target enzymes involved in the processing of sncRNAs or other components of the RNA-protein complexes they interact with, thereby modulating sncRNA activity. Advanced delivery systems, including viral vectors and nanoparticles, are also being explored to improve the therapeutic application of sncRNAs in cancer treatment [134].

3.6. Future perspectives of sncRNAs in gynecological cancers

The most probable future for sncRNAs in gynecological tumor cancers lies in the synergy between research and clinical applications. Many challenges are associated with understanding the precise sncRNA functions in gynecological malignancies. By achieving a more detailed comprehension of molecular mechanisms at the sncRNA-mediated level, it will be possible to examine tumor resistance features more thoroughly. A critical issue to address is the role of miRNA as a sensitive, distinctive, and prognostic biomarker [135]. Expanding sample cohorts and determining their prospective outcomes will significantly contribute to the established utilization of miRNA signatures in the management of gynecological cancer risk factors, including cancer screening, risk stratification, treatment selection, and monitoring treatment response. Additionally, miRNA mimics or anti-miRNAs delivered via nanoparticles can be utilized in precision medicine to restore dysregulated miRNA expression or inhibit oncogenic miRNA activity [136].

Research on tRFs in gynecological cancers offers a promising avenue for advancing our understanding of cancer biology. It is crucial to elucidate the specific roles of particular tRFs in gynecological cancer biology [97]. Functional studies in vivo and in vitro can reveal the interactions and regulatory roles of tRFs

in various cellular processes, including cell invasion, migration, apoptosis, and proliferation [137]. Furthermore, exploring the interactions between tRFs and other regulatory molecules, such as miRNAs and lncRNAs, can provide insights into the complex communication networks underlying cancer pathogenesis. Evaluating dysregulated tRFs as potential diagnostic, prognostic, or predictive biomarkers for gynecological malignancies is paramount. Developing robust and reliable methods for detecting and quantifying tRFs is essential for integrating them into clinical practice, thereby facilitating personalized patient care.

In addition, the exploration of piRNAs holds significant promise for advancing research in gynecological cancer. Investigating piRNAs can lead to a deeper understanding of cancer biology and result in more refined disease treatments. Developing specialized methodologies to elucidate the precise functions of piRNAs in gynecological cancer is crucial. Experimental approaches involving in vitro studies and animal models can elucidate the molecular mechanisms through which piRNAs regulate key cellular processes such as proliferation, apoptosis, migration, and invasion. Moreover, understanding the interplay between piRNAs, microRNAs, and long non-coding RNAs provides a comprehensive view of piRNA-mediated regulation in cancer. Aberrant expression patterns of piRNAs may serve as valuable biomarkers for the detection and diagnosis of gynecological malignancies, offering significant clinical utility [138]. Despite the importance of piRNAs in gynecological cancers, this area of research remains underexplored. Both *in vitro* and animal model experiments may provide further insights into the molecular mechanisms by which piRNAs regulate proliferation, apoptosis, migration, and invasion [139]. This exploration not only enhances our knowledge of cancer biology but also fine-tunes disease treatments.

Furthermore, nanoparticles hold promise as mimics or inhibitors of sncRNAs, facilitating the modulation of oncogenic miRNAs or tRFs activity or restoring normal miRNA or tRF expression [140]. Clinical studies involving laboratory-based work with large patient cohorts are necessary to identify which ncRNAs, such as piRNAs, are significantly involved in early detection, prognosis, or treatment processes. Developing next-generation, reliable assays for ncRNAs (e.g. piRNAs) will accelerate their clinical translation [141]. The implementation of ncRNA therapies within the clinical setting of gynecological cancer presents challenges but requires interdisciplinary collaboration and translational strategies to convert advanced technologies into clinically valuable interventions. Correspondingly, ncRNAs in gynecological cancers signify a progressive pathway for advancing cancer biology, diagnostics, prognostics, and treatment options, with collaborative efforts driving the field forward. The primary emphasis lies on interdisciplinary initiatives and translational approaches to effectively translate advanced technologies into practical clinical applications [142].

4. Diagnostic and prognostic applications of sncRNAs in gynecological cancers

The utilization of ncRNA amplification holds immense potential for enhancing diagnostic procedures in the screening of gynecological cancers. This approach enables the selection of patients based on disease severity and facilitates the customization of treatment strategies. The following paragraph examines the prospective roles of various ncRNAs, including miRNAs, tRFs, and piRNAs in the diagnosis of gynecological cancers. In specific, miRNAs have garnered attention due to their aberrantly altered expression levels and therefore their prognostic biomarker value for gynecological cancers. Research has demonstrated that miRNAs are specifically downregulated at various disease stages, enabling residual disease testing and prediction of patient outcomes. Signatures of miRNA expression have been detected not only in serum and plasma but also in cervical fluid, paving the way for the creation of noninvasive diagnostic assays [143]. Furthermore, miRNA expression profiles in tissue samples are utilized to identify histotypic and subtype patterns in gynecological malignancies [144]. Additionally, tRFs have emerged as a new group of tumor biomarkers associated with gynecological cancer stages and patients' responses to therapy. The tRF signatures can enhance the diagnostic sensitivity of various conditions and identify risk factors, ultimately leading to improved diagnostic protocols [145]. Similarly, piRNAs represent a relatively understudied field that identifies a novel group of diagnostic biomarkers useful for gynecological cancers. The close association between aberrant piRNA expression profiles and the development and progression of cancer suggests their potential utility as diagnostic and prognostic factors. piRNAs have the capacity to establish unique cancer signatures in tissues or fluids, complementing molecular biomarkers for diagnostic purposes [146]. Moreover, these piRNA patterns could serve as biomarkers for different cancer subsites and types of treatment, ushering in a new era of personalized cancer screening, particularly for females. By integrating clinical piRNA analysis into current diagnostic procedures, healthcare providers can achieve higher precision, reduce treatment durations for gynecological oncology patients, and improve outcomes.

The establishment of robust and reliable procedures for these methods is a crucial task, since it will transform them into widely applicable tools in translational medicine for diagnostic purposes [147]. The complexities of diagnosing gynecological cancers can be better understood through ncRNA research, which promises a broad and optimistic horizon in cancer molecular mechanisms and prognostic biomarkers. With this understanding, healthcare professionals will be better equipped to assess disease progression and design treatment plans, potentially improving survival rates. Recent studies have underscored the diagnostic value of sncRNAs (e.g. miRNAs, tRFs and piRNAs) in staging and prognosis of gynecological malignancies [96]. For instance, abnormal expression levels of miR-21 are associated with aggressive tumor behavior such as high neoplastic cell density, tissue invasion, and therapy resistance in ovarian malignancies. Conversely, reduced levels of miR-143 and miR-145 have been linked to increased cancer incidence, serving as potential diagnostic biomarkers for poor prognoses.

Furthermore, tRF-3001A has been demonstrated to correlate with increased metastatic potential and overall survival in ovarian cancer patients, highlighting the potential of tRFs as prognostic biomarkers [66]. This underscores tRFs' relevance in

understanding the progression and prognosis of gynecological cancers. Additionally, it's noteworthy that decreased levels of miR-200c and miR-205, which are tumor biomarkers, are associated with larger tumor sizes and lymph node metastases, providing prognostic insights into unfavorable cancer progression [148]. These findings underscore the importance of small non-coding RNAs, such as tRFs and miRNAs, in predicting disease outcomes and guiding therapeutic strategies in gynecological malignancies.

In endometrial cancer, research has revealed that dysregulated expression of tRFs, particularly elevated levels of 5'tRNA halves, play a crucial role in metastasis and treatment resistance in patients, positioning tRFs as significant predictive markers [149]. Studies have also focused on miRNA dysregulation and prediction in cervical cancer. Reduced levels of miR-143 and miR-145 have been associated with lymph node metastases and advanced disease stages, serving as predictive biomarkers [150]. Conversely, elevated levels of miR-21 are linked to higher recurrence rates and lower survival probabilities in cervical cancer patients [151]. Moreover, aberrant expression of piRNAs in patients with cervical cancer has been implicated in the development of more aggressive forms of the disease [120]. Specific piRNAs are being investigated as predictive biomarkers for disease progression and responsiveness to treatment [152].

Last but not least, it's important to note that cancer diagnosis and treatment have been significantly influenced by advancements in sequencing technologies [153]. Clinical applications of these technologies are evident through the use of gene panels, which involve sequencing a group of genes traditionally associated with cancer [154]. This molecular sequencing technique provides a comprehensive, genome-wide characterization of genes implicated in various types of malignancies, including gynecological cancers, revealing detailed molecular alterations underlying tumorigenesis [155,156]. Gene panels typically include crucial oncogenes, tumor suppressor genes as well as genes involved in DNA repair pathways, targeting clinically relevant mutations within this spectrum. Among these genes that play pivotal roles in carcinogenesis and therapeutic response, *TP53*, *BRCA1*, *BRCA2*, *EGFR*, *KRAS*, *ERBB2* should be stated [157]. After many years of ncRNA research, several miRNAs (e.g. miR-378a-3p, miR-374a-5p) have been added to these panels as potential biomarkers [158,159]. Of note, while individual biomarkers may exhibit high sensitivity in predicting tumors, they often lack specificity. In contrast, a panel of biomarkers can provide a more accurate diagnostic outcome [159]. This advancement accelerates the diagnostic process, enabling healthcare professionals to decipher the complex molecular networks driving abnormal cancer development.

The mentioned ncRNA biomarkers offer valuable insights into the potential molecular mechanisms underlying disease progression and treatment responses. However, the evaluation of these biomarkers is poised for prospective trials, marking the next phase in this research cycle and the challenging task of establishing them in standard clinical practices [160]. Moving forward, the implementation of rigorous clinical trials will be crucial to validate the efficacy and reliability of these ncRNA biomarkers. This process will determine their utility in guiding personalized treatment strategies and improving overall patient management in gynecological cancers and beyond.

5. sncRNAs as predictive biomarkers in gynecological cancers

In the context of gynecological cancers, sncRNAs have emerged as promising biomarker candidates (Table 2) [161]. In particular, miRNAs have shown great promise as predictive biomarkers for treatment response [162]. Indicatively, miR-21 is frequently overexpressed in ovarian cancer and correlates with tumor progression, metastasis, and resistance to chemotherapy [163]. Similarly, elevated levels of miR-21 are associated with progression, invasion, and metastasis in cervical cancer [151]. In cervical cancer, the downregulation of miR-143/145 is implicated in disease initiation and progression [164]. Reduced levels of miR-200c and miR-205 are linked to advanced stage and poor outcomes in endometrial cancer, with miR-205 specifically associated with tumor aggressiveness and metastasis [165]. Moreover, elevated miR-21 levels promote invasion, migration, and metastasis in vulvar cancer cells [166]. Conversely, repression of miR-34a expression characterizes squamous cell carcinoma of the vulva and is associated with impaired cell cycle control and apoptosis

Table 2. Overview of the sncRNA roles in gynecological cancers, highlighting their potential as diagnostic biomarkers, prognostic indicators, and contributors to drug resistance.

sncRNA type	Diagnostic Potential	Prognostic Potential	Role in Drug Resistance
miRNAs	Biomarkers for early detection; altered expression correlates with cancer type (e.g. miR-200 family in ovarian cancer)	Predict survival outcomes (e.g. miR-21 in cervical cancer)	Contribute to chemoresistance by targeting genes involved in drug metabolism and apoptosis (e.g. miR-200c in ovarian cancer)
piRNAs	Potential biomarkers due to differential expression patterns across cancer stages. (e.g. piR-651 in cervical cancer)	Correlate with disease progression and metastasis (e.g. piR-651 in endometrial cancer)	Involved in drug resistance mechanisms by modulating gene expression related to drug efflux and cell survival pathways. (e.g. piR-52200 in ovarian cancer)
lncRNAs	Expression profiles indicative of cancer subtypes; dysregulation associated with tumor aggressiveness (e.g. HOTAIR in cervical cancer).	Predict recurrence and metastasis (e.g. MALAT1 in endometrial cancer).	Contribute to drug resistance by regulating signaling pathways involved in proliferation and survival (e.g. HOTAIR in ovarian cancer).
circRNAs	Altered expression in cancer tissues compared to normal; potential tissue-specific biomarkers (e.g. circHIPK3 in ovarian cancer).	Correlate with patient outcomes and response to therapy (e.g. circEIF4G2 in cervical cancer).	Involved in drug resistance mechanisms by acting as miRNA sponges and regulating target gene expression (e.g. circMTO1 in ovarian cancer)

[167]. The dysregulation of miRNA patterns has been linked to resistance or sensitivity of tumor cells to various therapies, including chemotherapy, targeted drug therapy, and immunotherapy [168].

Besides miRNAs, aberrant expression levels of tRFs frequently play a role in modulating the response of cancer cells to various therapeutic interventions, including chemotherapy, targeted therapy, immunotherapy as well as other anti-tumor drugs [169]. Notably, dysregulated levels of tRF-03357 and tRF-03358 have been correlated with cancer progression and metastasis in ovarian cancer [94]. Although there is still limited data on the function of 3′ tRNA halves (tiRNAs) in gynecological diseases, they are recognized as potential contributors to carcinogenesis by influencing crucial cellular processes, including cell cycle regulation, apoptosis, DNA damage response, and drug resistance mechanisms [95,170]. The profiles of tRFs associated with treatment responses in ovarian, endometrial, and cervical cancers suggest that understanding these mechanisms could provide insights into drug resistance mechanisms and potentially lead to more targeted treatment options [171]. By elucidating how specific tRFs influence these pathways, researchers aim to enhance therapeutic strategies tailored to the molecular characteristics of gynecological cancers, thereby improving patient outcomes.

Research into piRNAs as predictive biomarkers and contributors to disease mechanisms is gaining significant traction, promising potential clinical applications. For instance, in vulvar squamous cell carcinoma (VSCC), elevated expression of piR-823 has been associated with an aggressive tumor phenotype and poorer clinical outcomes [172]. Similarly, overexpression of piR-651 has been observed in ovarian cancer, suggesting its role in tumor growth and metastasis through post-transcriptional or epigenetic modifications [161]. In cervical cancer, elevated levels of piR-54265 have been detected compared to adjacent normal tissues, suggesting its involvement in cancer progression by influencing critical signaling pathways related to cell proliferation, invasion, and metastasis [173,174]. Studies have also indicated that piRNAs may be dysregulated in treatment-resistant profiles, while others may predict responses to specific therapies in ovarian, endometrial, and other gynecological cancers [96]. These findings highlight the potential of piRNAs as biomarkers for predicting treatment outcomes and guiding personalized therapeutic strategies in gynecological cancers. Further research into the precise roles and mechanisms of piRNAs in these malignancies is crucial for improving clinical interventions and patient care.

The identification of ncRNAs, particularly miRNAs, has indeed revolutionized the potential for new diagnostic biomarkers in gynecological malignancies, paving the way for personalized therapeutic approaches and improved treatment outcomes. However, despite the promising findings so far, further validation studies and prospective trials are essential to establish the clinical utility of ncRNA predictive biomarkers and integrate them into routine clinical practice [173].

5.1. sncRNAs and clinical trials in gynecological cancers

Today, sncRNA-based therapeutics are gaining significant attention for their potential in treating various gynecological malignancies and enabling personalized therapies. However, like other emerging treatments, they face limitations, particularly in delivery, specificity, and safety, which restrict their current use in clinical trials [175]. Studies have shown a correlation between sncRNA and gynecological cancers, suggesting that while clinical trials are still relatively few, their number is increasing, including trials focused on tRFs [49]. Most of this research remains at the preclinical level, aiming to understand the mechanisms of these molecules and their potential as drug targets. For example, the phase I clinical study of the miR-34 mimic (MRX34) for treating various carcinomas, including gynecological cancers, has not been included [176]. Ongoing progress in these trials and continuous research into delivery methods and the anticancer properties of sncRNAs will likely pave the way for future clinical trials in gynecologic tumors.

6. Conclusion

Investigation of ncRNAs, previously overlooked as transcriptional byproducts, has revealed their pivotal role in gene regulation and their strong implications in various types of cancer, including cervical, endometrial, and ovarian. While our knowledge of piRNAs and tRFs remains limited, miRNAs have garnered significant attention with several studies progressing toward clinical applications, including ongoing trials for ovarian and endometrial cancers [177]. Since miRNAs are detectable in blood, they show great promise as early diagnostic and prognostic biomarkers for various malignancies. However, challenges include the need for comprehensive evaluation across diverse patient cohorts to enhance the applicability and reliability of these biomarkers. As we deepen our understanding of the distinct sncRNA types and their specific target networks, we can refine their potential roles in diagnostics and therapeutic strategies [147]. One of the critical factors contributing to increased cancer-related deaths, such as in ovarian cancer, is delayed diagnosis and the development of drug resistance. Elucidating the roles of sncRNAs in cancer diagnosis and therapy, promises to enable early detection and timely therapeutic interventions, marking a significant advancement in the management of gynecological malignancies. Continued research and clinical validation efforts are essential to harness the full potential of ncRNAs in transforming cancer care outcomes.

7. Expert opinion

ncRNAs represent a diverse array of RNA molecules, garnering recent attention as potentially critical regulators of tumor cell progression. Widely expressed across various tumors, including gynecological malignancies, ncRNAs function as intricate cellular constituents. Recent research highlights their involvement as mediators in signaling pathways within tumors, where they interact with other RNAs or proteins to influence cancer development and progression. This review focuses on the utility of sncRNAs, such as miRNAs, tRFs and piRNAs, in the context of diagnostic, prognostic and predictive applications in gynecological cancers. These ncRNAs have demonstrated a noteworthy potential as biomarkers due to their specific

expression patterns in distinct cancer types and stages, providing new insights into tumor biology and aiding in clinical decision-making. For instance, miRNAs are known to regulate gene expression post-transcriptionally, being implicated in various aspects of cancer biology, including proliferation, metastasis, and drug resistance. Similarly, tRFs and piRNAs exhibit regulatory functions that may influence cancer cell behavior and treatment response. The objective of this review is to advance our understanding of how these sncRNAs contribute to tumor biology and their potential translation into clinical practice. By unraveling their roles in cancer pathogenesis and progression, researchers aim to develop novel diagnostic tools and therapeutic strategies that could improve patient outcomes in gynecological cancers. Continued exploration and validation of these ncRNA biomarkers are crucial steps toward realizing their clinical utility and thus their integration into routine cancer care protocols.

The functional involvement of ncRNAs in gynecological cancers represents a significant advancement in our understanding of these complex diseases. Known for their role in regulating gene expression and cellular processes, ncRNAs have emerged as pivotal players that offer crucial insights into disease mechanisms and potential targets for cancer therapies. In gynecological cancers, ncRNAs exhibit widespread dysregulation, making them promising candidates for clinical applications. They can aid in early diagnosis by serving as specific biomarkers that discriminate cancerous from healthy tissues. Additionally, ncRNAs can stratify patients based on their risk profiles, guiding tailored treatment strategies that optimize therapeutic outcomes. Their utility extends to predictive purposes, where they may indicate responsiveness to certain treatments or predict disease recurrence. Beyond diagnostics and prognostics, ncRNAs open new avenues for therapeutic interventions in gynecological cancers. RNA-based therapies, such as miRNA mimics, nanoparticles delivering ncRNAs, small molecule inhibitors targeting ncRNA pathways, and immunotherapies utilizing ncRNA modulation, represent promising strategies. These approaches aim to modulate cancer cell behavior, enhance treatment efficacy, and potentially overcome drug resistance. However, realizing the full clinical potential of ncRNAs requires addressing several challenges. Standardizing methodologies for identifying and validating relevant ncRNAs in vast datasets generated by bioinformatics tools is essential. Robust implementation of these findings using advanced technologies and bioinformatics pipelines is crucial to translate ncRNA discoveries into clinical practice effectively. In conclusion, the discovery of ncRNAs' functional roles in gynecological cancers offers transformative opportunities in precision oncology. By leveraging ncRNAs as diagnostic and therapeutic tools, clinicians can advance toward personalized healthcare, improving patient outcomes and quality of life. Continued research and interdisciplinary collaboration will be crucial in exploiting the full ncRNA potential and thus their integration into clinical practice.

The incorporation of sncRNA biomarkers into clinical practice is expected to enable physicians to design and implement treatments based on the genomic profiles of each patient's tumor. Undoubtably, a key step is the establishment of standardized protocols, validation of ncRNA panels across diverse patient groups as well as the development of precise diagnostic assays to bridge the gap between treatment expectations and clinical outcomes. Collaboration among scientists, bioinformaticians, and industry stakeholders is essential for advancing ncRNA research. Interdisciplinary partnerships enhance research quality, expedite discoveries and facilitate the translation of ncRNA-based therapies and diagnostics into clinical use. Through these collaborative efforts, researchers will be able to fully harness the potential of ncRNA biomarkers as diagnostic, prognostic, and predictive tools in managing gynecological cancers.

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•• **Articles of considerable interest. These studies provide an overview of the sncRNA roles under normal and cancer conditions.**

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