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Mini-review

# MicroRNAs in gynecological cancers: Small molecules with big implications

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ABSTRACT

Gynecological cancers (GCs) are often diagnosed at advanced stages, limiting the efficacy of available therapeutic options. Thus, there remains an urgent and unmet need for innovative research for the efficient clinical management of GC patients. Research over past several years has revealed the enormous promise of miRNAs. These small non-coding RNAs can aid in the diagnosis, prognosis and therapy of all major GCs, viz., ovarian cancers, cervical cancers and endometrial cancers. Mechanistic details of the miRNAs-mediated regulation of multiple biological functions are under constant investigation, and a number of miRNAs are now believed to influence growth, proliferation, invasion, metastasis, chemo-resistance and the relapse of different GCs. Modulation of tumor microenvironment by miRNAs can possibly explain some of their reported biological effects. miRNA signatures have been proposed as biomarkers for the early detection of GCs, even the various subtypes of individual GCs. miRNA signatures are also being pursued as predictors of response to therapies. This review catalogs the knowledge gained from collective studies, so as to assess the progress made so far. It is time to ponder over the knowledge gained, so that more meaningful pre-clinical and translational studies can be designed to better realize the potential that miRNAs have to offer.

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## Introduction

Gynecological cancers (GCs) are the cancers that originate from, and affect, women's reproductive organs such as cervix, ovary, uterus/endometrium, vagina and vulva. GCs originate in different places within a woman's pelvis, the area between the hip bones and below the stomach. Each GC is unique, with its own signs and symptoms, as well as risk factors. The risk for GCs increases with age. In the United States (US), almost 90,000 women are diagnosed with GCs every year, and more than 28,000 women die from these malignancies [1]. Among the different GCs, ovarian, cervical and endometrial cancers are the most frequent and, thus, considered major women health issues. Although endometrial cancer (EC) is the most common GC among women, ovarian cancer (OC) is the most lethal type [2], and despite scientific advancements, mortality rates of GCs continue to rise [1]. Both early diagnosis and limited treatment options for advanced GCs are contributing factors to their high mortality, emphasizing the need for further advancements in these areas.

Recent years have witnessed growing interest in the field of microRNAs (also referred to as miRNAs/miRs) because of their potential to regulate diverse biological processes [3]. MicroRNAs are small, non-coding RNA molecules, approximately 20–22 nucleotides in length. In general, miRNAs regulate the expression of genes by binding to the 3′-untranslated regions (3′-UTRs) of target messenger-RNAs (mRNAs) with partial or full complementarity, resulting in either translational repression or degradation of target mRNAs [3]. Human genome encodes several thousand miRNAs and the knowledge about their identity and functions is constantly emerging. It is believed that miRNAs regulate the expression of more than one-third of all human genes [4]. In this review article,

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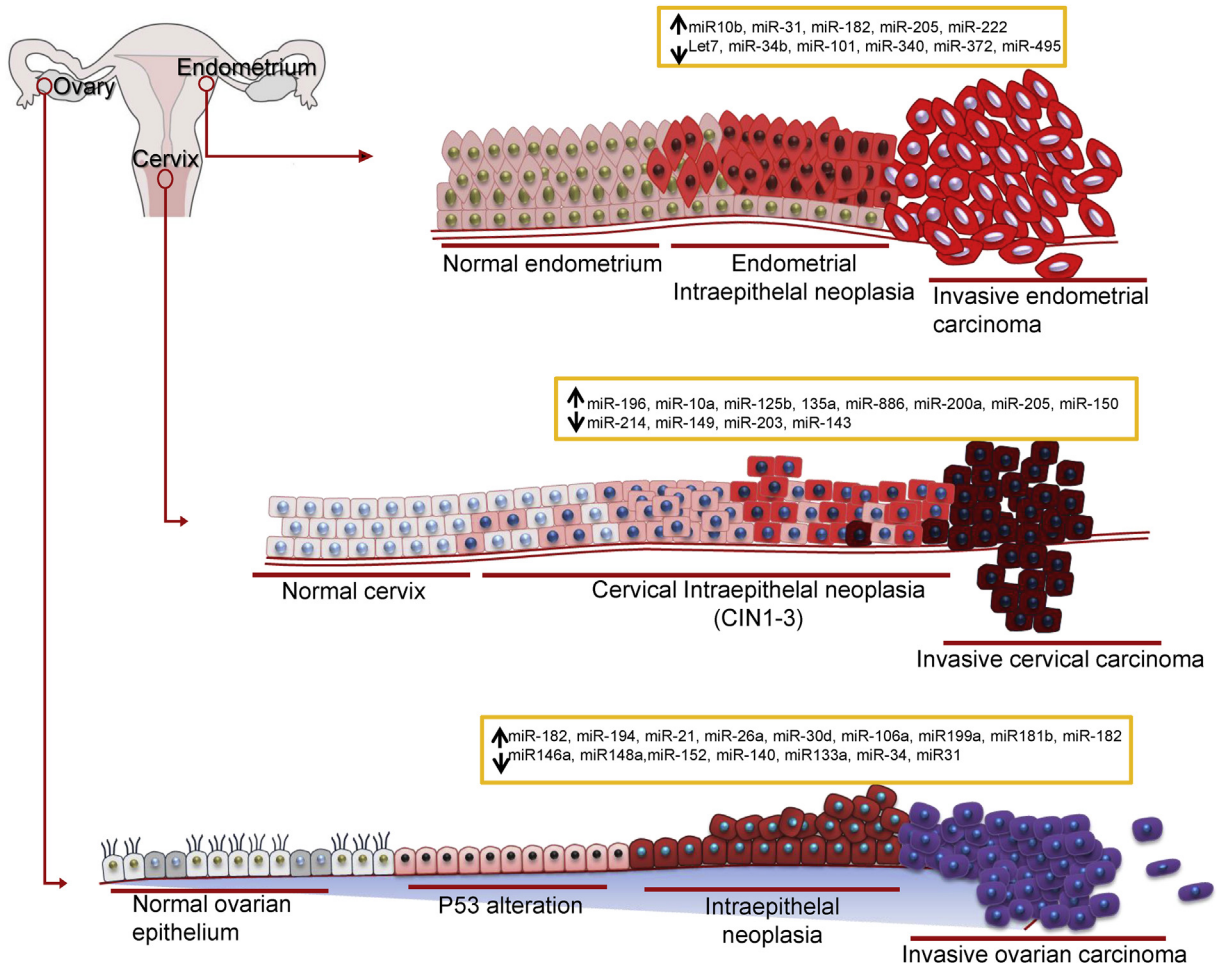


**Fig. 1.** Role of miRNAs in the development and progression of gynecological malignancies. During the progression of gynecological cancers (ovarian cancers, cervical cancers and endometrial cancers), miRNAs are highly dysregulated. Tumor suppressor miRNAs are either lost or their expression down-regulated at the initiation stages, while oncogenic miRNAs get up-regulated, facilitating the progression of disease. The miRNAs identified in this figure are only representative and a comprehensive list is available in the individual tables.

we discuss deregulation of miRNAs in GCs, their established or putative functions, and clinical and translational relevance. Considering the high incidence and mortality, we will mainly focus on ovarian, cervical and endometrial cancers as the representative GCs.

## Dysregulation of miRNAs in gynecologic cancers

Dysregulation of miRNAs in GCs has been reported in multiple studies suggesting their pathobiological importance. Here, we discuss some of these reports on the differential expression of miRNAs in ovarian, cervical and endometrial cancers and highlight their significance in the development and progression of gynecological malignancies (Fig. 1, Table 1).

### *Ovarian cancer*

OC is the deadliest GC in the US [5] (Table 2). Approximately seventy percent of the patients with OC are diagnosed with advanced disease [6], resulting in poor prognosis, even with aggressive and immediate treatments. Several studies have reported miRNA profiling from serum, plasma and tissues of OC patients, and have successfully identified distinct miRNA signatures. Zhang et al. were the first to demonstrate differential expression of miRNAs in OC [7]. Their study identified a copy number loss of the regions that harbor miR-15a and miR-16-1 in 23.9% of OC cases. Using deep sequencing of samples from normal and malignant ovarian tissues, Wyman et al. discovered six novel differentially-expressed miRNAs (miR-2114*, miR-2115*, miR-2116*, miR-2114*, miR-449* and miR-548q) [8]. In addition, their study also identified miRNAs that were differentially expressed in OC histologic subtypes. miR-449a was specific to serous, miR-499-5p/miR-375/miR196a/miR-196b/miR-182 were specific to endometrioid, and miR-486-5p/miR-144/miR-30a/miR-199a-5p were specific to clear cell carcinoma [8]. Based on miRNA microarray data obtained from analysis on normal ovarian surface epithelium and ovarian tumors, Shahab and coworkers identified forty-two miRNAs, out of which thirty-three were over-expressed and nine miRNAs were down-regulated in OC [9]. In a recent study, small RNA sequencing was performed on normal tubal and high-grade serous ovarian cancer samples leading to identification of differential expression of several miRNAs, of which 59 were known and 20 were novel [10]. Another recent study identified 1156 deregulated miRNAs in OC [11]. miR-1, miR-133a, and miR-451 were under-expressed while miR-141, miR-200a, miR-200c, and miR-3613 were significantly elevated in most of the OC patients. Resnick et al. investigated differentially expressed miRNAs in the serum of OC patients, and observed that miR-21, miR-29a, miR-92, miR-93 and miR-126 were significantly over-expressed, while miR-155, miR-127 and miR-99b were under-expressed [12]. From the plasma of patients with OC, a specific miRNA signature was detected. This included nineteen down-regulated and three over-expressed miRNAs in OC patients, as