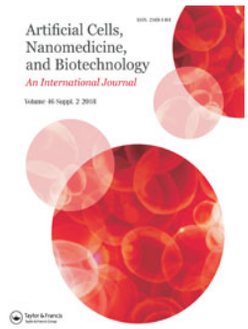

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The role of microRNAs and nanoparticles in ovarian cancer: a review

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ABSTRACT

MicroRNAs (miRNAs) have had a revolutionary impact on cancer research over the recent years. They emerge as important players in tumourigenesis, leading to a paradigm shift in oncology. Ovarian cancer is the leading cause of death among gynaecologic malignancies. Therefore, there is a strong need for prognostic and predictive markers for early diagnosis which helps optimize and personalize treatment. Asymptomatically, ovarian cancer is often diagnosed at advanced and incurable stages. Efficient targeting and sustained release of miRNAs/anti-miRNAs using nanoparticles conjugated with antibodies and/or peptides could reduce the required therapeutic dosage while minimizing systemic and cellular toxicity. Given miRNAs importance in clinical oncology, here we focus on the development of miRNA nanoformulations to achieve enhanced cellular uptake, bioavailability and accumulation at the tumour site. Although many obstacles need to be overcome, miRNA therapy could be a powerful tool for ovarian cancer prevention and treatment. In this review, we discuss about the emerging roles of miRNAs in various aspects of ovarian cancer.

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Introduction

Nanotheranostic agents are applied in different types, such as gold, silver and magnetic nanoparticles (NPs), along with nanoshells and nanocages that can be conjugated to biological and conventional therapeutics (drugs, ligands and antibodies) to enhance delivery rate and efficiency of therapy. Nanotheranostics are now being widely used for targeted drug/aptamers delivery, as well as diagnostic imaging of the various stages of diseases (by MRI, CT scan, ultrasound etc) [1].

Cancer is one of the most common causes of death worldwide, and has become a major public health challenge [2]. Epithelial ovarian cancer (EOC) is the second most common gynaecological cancer with a 5-year survival rate of only 30% in advanced stages [3,4]. Worldwide ovarian cancer metastatized into extra-abdominal regions is the second most encountered gynaecologic cancer [5]. A 5-year survival rate for individuals diagnosed with advanced cervical, colorectal, kidney or pancreatic cancer is better than ovarian cancer [6]. EOC is a life-threatening disease determined by late-stage presentation and high pathological and molecular heterogeneity [7]. The standard treatment for EOC is aggressive primary surgery followed by platinum-based chemotherapy [8]. Ovarian cancer is an important leading cause of death due to gynaecologic malignancies among women in developed countries [9]. High-grade serous ovarian cancer (HGSOC) accounts for 70–80% of ovarian cancer deaths [10]. Accumulating evidence has revealed that microRNAs (miRNAs or miRs) are extensively involved in cancer progression and suppression by regulating thousands of cancer-associated genes [11]. Circulating cell-free miRNAs have been shown to have the potential to be considered as new biomarkers in cancer diagnosis, predict prognosis and response to therapy [12].

MiRNAs, biogenesis and functions

The identification of miRNAs and their mechanism of action was originally made in the nematode *Caenorhabditis elegans* [13].

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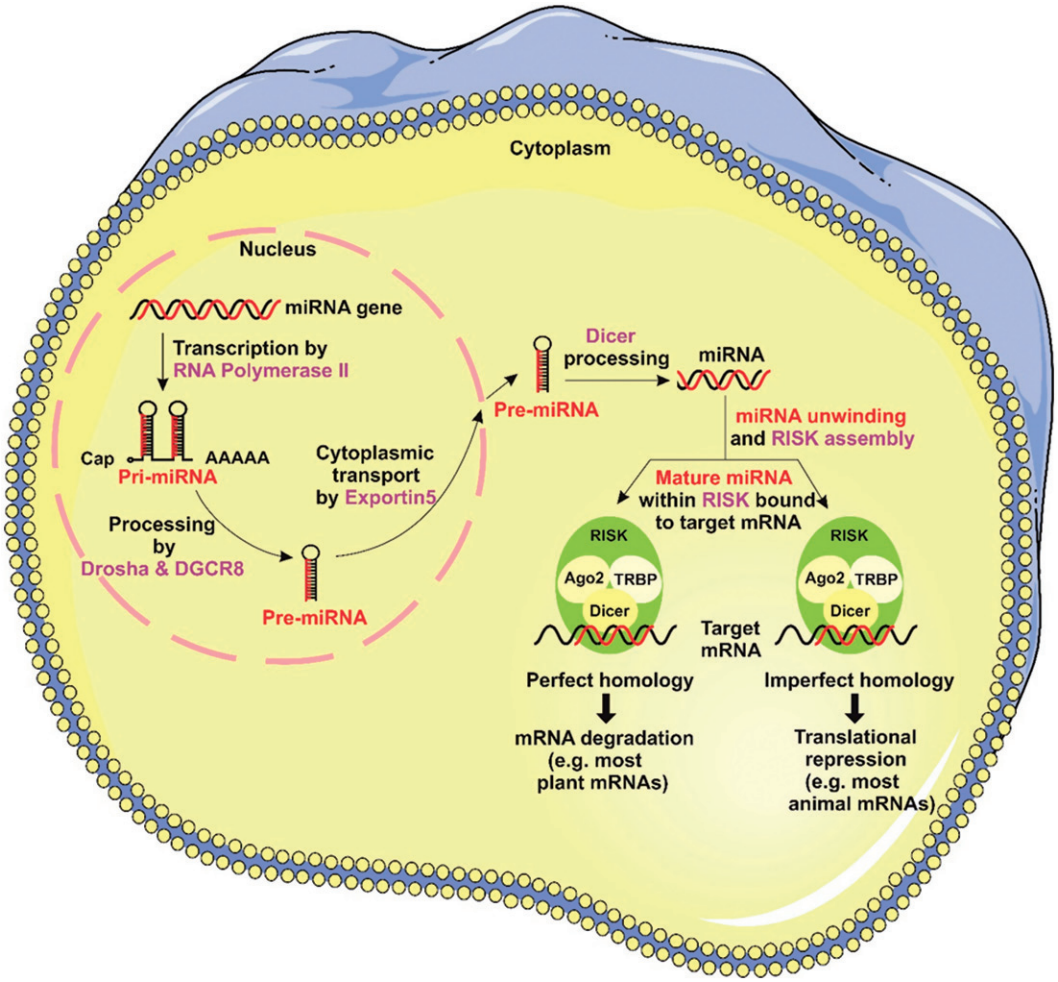

Figure 1. miRNA biogenesis and mechanisms of gene silencing (see text for details).

The first miRNA was discovered in 1993, but additional insights for miRNAs mode of action required simultaneously published work by Ruvkun's team [13]. Under a standard nomenclature system, names are assigned to experimentally confirmed miRNAs before publication [14,15]. The prefix "miR" is followed by a dash and a number, the latter often indicating order of naming. For example, miR-124 was named and likely discovered prior to miR-456. A capitalized "miR-" refers to the mature form of the miRNA, while the non-capitalized "mir-" refers to the pre-miRNA and the pri-miRNA, and "MIR" refers to the gene that encodes them [16].

A miRNA is a small non-coding endogenous RNA molecule (containing about 22 nucleotides) found in plants, animals and some viruses, which has functions in mRNA silencing and post-transcriptional regulation of gene expression [17]. MiRNAs directly interact with partially complementary sites located in the 3′ untranslated region (3′UTR) of target mRNAs and repress their translation [18]. More than 60% of all mRNAs are estimated to contain miRNA target sites at their 3′UTR region, suggesting a tight regulation as well as their involvement in normal cellular homeostasis and in diseased states [19]. To date, 940 human miRNAs have been identified, which are annotated and catalogued in a searchable Web-based miRNA database known as miRbase [20]. Out of 232 mammalian miRNAs analyzed, 40% existed within introns of coding RNA, 10% within introns of noncoding RNA (ncRNA) and 13% within exons of ncRNA. In addition, a small portion of miRNAs exists within exons (mainly 3′UTR) of coding "host" genes, some of which are expressed from the same transcriptional unit. The remaining miRNAs are intergenic, with mostly undefined transcriptional units as of yet. For that purpose, computational tools were developed for prediction of miRNA core promoters [21].

The pre-miRNAs are assembled in large protein complexes known as RNA-inducing silencing complex (RISC or miRISC). One of the known proteins that form RISC is RNA-specific endonuclease Dicer, which is involved in the processing of pre-miRNA into the mature form [22]. Each RISC or miRNA ribonucleoprotein complex) miRNP (contains a member of the Argonaute (Ago) protein family; the Ago protein probably binds directly to the mRNA in these complexes, although there is no evidence for this. The Ago protein has four isoforms which only Ago2, also known as "slicer," has the capacity to cleave the target mRNA [23] (Figure 1).

Identifying the mRNA targets of miRNAs

Many methods have been proposed to identify miRNAs targets [24]. Initially experimental methods have focused on the effects of miRNA–target interactions at levels that range from broad phenotypes to changes in the frequency of mRNAs

and proteins. More recently, methods to directly capture Ago-bound RNAs have become available (Figure 1) [25].

miRNA and cancer

MiRNAs are generally involved in post-transcriptional gene regulation. They are highly conserved among a wide range of species [26]. MiRNAs are key regulators of cellular pathways, and they appear to play an important role in tumourigenesis [27]. Several studies have documented the implication of miRNAs in nearly every carcinogenesis process, including tumour development, apoptosis, invasion and metastasis, as well as anticancer drug resistance [28]. Currently, it is well known that miRNAs can be upregulated or downregulated in various human cancers. Overexpressed miRNAs may have functions as oncogenes by downregulating tumour suppressor genes, whereas the downregulated miRNAs may act as tumour suppressor genes by negatively regulating oncogenes [29]. Important insights into the functions of miRNAs in cancer have been provided through the demonstration involved in known oncogenic pathways. Human RAS oncogene family (H-, K- and N-RAS) contains binding sites for the let-7 family of miRNAs in their 3′UTR [30]. miR-221 from complex samples is demonstrated in the total RNA isolated from human prostate cancer cells and xenografts [31]. A combination of upregulated miR-155 and downregulated miR-141 is found to result in a 97% overall correct classification of the matched malignant and non-malignant tissue samples [32]. By calculating the differences between delta cycle thresholds (Ct) of miR-503 and miR-511, adrenocortical carcinomas are significantly distinguished from benign adenomas with high sensitivity and specificity. These miRNAs may be considered as helpful biomarkers for the diagnosis of adrenocortical malignancy [33].

MiR-221 and miR-222 are examples of miRNAs that act as oncogenes. They exert oncogenic functions by targeting and inhibiting the expression of the tumour suppressor gene p27Kip [34]. There is also evidence of possible role of miRNAs in p53-induced cell death. For example, p53-mediated upregulation of miR-34 is known to induce cell death in *C. elegans* as well as in mammalian cells. Many other miRNAs other than miR-34 family members are now known to be regulated by p53, viz., miR-194, miR-207, miR-107, miR-215, miR-192, miR-16–1, miR-143, miR-145 and miR-216 [35]. It has been shown that p53 transcriptionally induces miR-34 expression, and this induction is important in p53-mediated apoptosis of cancer cells [36,37]. In the study of chronic lymphocytic leukemia (CLL), low expression of miR-29 b, miR-29c, miR-181 family, and miR-223 was found to be strongly associated with disease progression in CLL cases harboring 17p deletion, whereas high expression of miR-181a in those harboring trisomy 12 suggested more aggressive disease. These biomarkers may be clinically useful to assess the tumour behavior in CLL [38]. It provided evidence that the relative concentration of miR-155 in serum significantly discriminated primary breast cancer patients from healthy women. Within the primary breast cancer cohort, patients at advanced tumour stages had significantly higher miR-34a than patients at early tumour stages. In the metastatic patients, miR-10b, miR-34a and miR-155 were correlated with the presence of overt metastases. miR10b is down-regulated in breast tumour tissue compared with normal breast tissue [39].

miRNAs and ovarian cancer

Numerous studies have shown that dysregulation of miRNAs is involved in a wide variety of human diseases including ovarian cancer [40]. The Cancer Genome Atlas (TCGA) project analyzed mRNA expression, miRNA expression, promoter methylation, and DNA copy number in a total of 489 HGSOCs and showed that ovarian cancer could be separated into 3 miRNA subtypes [41] miR-200, a family of tumour suppressor miRNAs, consisting of miR-141, miR-200a, miR-200 b, miR-200c and miR-429, is significantly involved in the inhibition of epithelial-to-mesenchymal transition (EMT), repression of cancer stem cell self-renewal and differentiation, modulation of cell division and apoptosis, and reversal of chemoresistance [42]. Hence, the miR-200 family miRNAs may act as master regulators in ovarian cancer by targeting some cancer-related genes [43]. High expression of miR-200c may predict improved survival in women with ovarian cancer [44].

Recent evidence indicates that miRNAs play important roles in various pathways related to anticancer drug resistance, e.g. influencing the response to the conventional chemo-agents cisplatin and microtubule-targeting drugs [2,45]. In ovarian cancer, 11 miRNAs were upregulated (miR-16, miR-20a, miR-21, miR-23a, miR-23b, miR-27a, miR-93, miR-141, miR-200a, miR-200b and miR-200c) and 12 miRNAs were downregulated (miR-10b, miR-26a, miR-29a, miR-99a, miR-100, miR-125a, miR-125b, miR-143, miR-145, miR-199a, miR-214 and let-7b) [46].

TCGA project has analyzed mRNA/miRNA expression, promoter methylation and DNA copy number in a total of 489 high-grade serous ovarian adenocarcinomas [47] and reported that high-grade serous ovarian cancer was characterized by TP53 mutations in almost every tumour (96%). In addition, there was a low but statistically significant prevalence of recurrent somatic mutations in 8 other genes including NF1, BRCA1, BRCA2, RB1 and CDK12. They also showed that ovarian cancers could be separated into 4 transcriptional subtypes, 3 miRNA subtypes and 4 promoter methylation subtypes. Integrated genomic analysis revealed a miRNA-regulatory network that defined a robust integrated mesenchymal subtype associated with poor survival in 459 cases of serous ovarian cancer and 560 cases independent of cohort data [48]. Eight key miRNAs (miR-25, miR-29c, miR-101, miR-128, miR-141, miR-182, miR-200a and miR-506) were identified and predicted to regulate 89% of the targets in this network. Recently, Davidson et al. summarized the clinical and diagnostic roles of miRNAs in ovarian carcinoma in their review of approximately 100 publications [49]. In addition, various miRNAs have also been identified as potential prognostic indicators, and promise utility in future practice. Mentioned studies are summarized in Table 1. A panel of 74 overexpressed and 49 underexpressed miRNAs in ovarian cancer was compared to ovarian surface epithelium (OSE) which was identified in another study, as well as histotype-specific signatures [58]. A panel of 42 miRNAs differentiating ovarian

Table 1. Circulation miRNAs as potential diagnostic biomarker for ovarian cancer.

Sample	Elevated miR	Decreased miR	Reference	Tumour histology
Plasma	miR-200b		[50]	
Plasma		Let-7f	[51]	
Serum	miR-21		[52]	
Serum	miR-221		[53]	
Plasma		miR-1290	[54]	
Serum	miR-429		[55]	
Serum	miR-141	miR-200c	[51]	
Serum		miR-145	[56]	
Exosomal	miR-21		[57]	
	miR-23b			
	miR-29a			

cancer from OSE was found by Shahab et al., of which 33 and 9 miRNAs were overexpressed and under-expressed in ovarian cancer, respectively. The authors found only infrequently negative association between miRNAs and their targets [59].

MiRNA expression profiles in high grade serous ovarian cancers

Paola et al. showed that miR-1246 was significantly up-regulated in the serum of patients with HGSOC compared to healthy individuals [60]. Eun Ji Nam et al. analyzed the miRNA expression profiles of 20 serous ovarian cancer tissues using a two-color system. The up-regulated miRNAs ($n = 11$) included miR-200a, miR-200b, miR-200c, miR-20a, miR-21, miR-23a, miR-23b, miR-27a, miR-141, miR-16 and miR-93, and the down-regulated miRNAs ($n = 12$) were miR-214, miR-26a, miR-29a, let-7b, miR-100, miR-10b, miR-125a, miR-125b, miR-143, miR-145, miR-199a-AS and miR-99a. Of these miRNAs, the most frequently up-regulated miRNA was miR-21 (17 of 20 cases), and the most frequently down-regulated miRNA was miR-125b [61].

In other reports that compared miRNA expression in ovarian cancers and normal ovarian tissues [17–19], five miRNAs were down-regulated (miR-140–3p, miR-143–5p, miR-34b-5p, miR-34c-5p and miR-145) and three were up-regulated (miR-96, miR-15b and miR-16) [62,63]. Downregulation of miR-34a/b/c, miR449b, miR-503 and miR-507 has been observed in late stage and high grade ovarian cancers [64,65]. Petrillo et al. showed that the expression levels of some miRNAs were associated with prognosis. They observed that miR-181a-5p, miR-199a-5p and miR-199a-3p were more expressed in tumours of patients with PFI <6 months, with residual tumour >1 cm, and their expression levels were associated to patients' survival [66].

Clinical relevance of cell-free miRNAs in ovarian cancer

About 20 studies have explored the diagnostic miRNAs in ovarian cancer. Taylor et al. showed the elevation of miR-21, miR-141, miR-200a, miR-200b, miR-200c, miR-203, miR-205 and miR-214 in ovarian cancer patients. These miRNAs were over-expressed even in patients with early stages of ovarian cancer. The miRNA signatures from exosomes were equivalent from the originating tumour cells, indicating that circulating miRNA profiles precisely reflected the tumour profiles [67]. Following this study, a variety of reports have confirmed the diagnostic potential of circulating miRNAs in body fluids such as serum, plasma, whole blood and urine [68–70] as summarized in Table 1.

miRNAs in ovarian cancer progression; nano and ovarian cancer

miRNAs are also used for prognosis and therapy in cancer [71]. The clinical application of miRNAs has rapidly matured from aspirational to now exploiting its diagnostic and therapeutic potential. We refer the reader to the comprehensive reviews describing the mechanisms of miRNAs action [72]. The study demonstrated that *in vivo* nano-liposomal delivery of miR-15a and miR-16 decreased tumour growth in preclinical chemo-resistant orthotopic ovarian cancer mouse model in support of combination therapies [73].

Over the past decade, nanotechnology has received remarkable attention for cancer therapy. At the molecular level, treatment with AuNPs has been shown to alter the profiles of a series of secretory cytokines [74]. AuNPs can efficiently mute single gene expression, quite similarly like a traditional siRNA; but alternatively, they can also be used in targeting and silencing siRNA (exogenous) and miRNA (endogenous) [75]. Dendrimer-grafted nano conjugated with gadolinium, which possesses a positively-charged nanosurface, can be used to interact with the negatively charged Let–7g miRNA (MIRLET7G, a putative RNAi agent), thereby forming Gd-NGO/Let–7g complexes, that demonstrated antineoplastic properties. Gd-NGO has also been shown to effectively carry the anthracycline anticancer drug epirubicin (EPI). Conjugation of MIRLET7G and EPI with Gd-NGO (Gd-NGO/Let–7g/EPI) enhanced the inhibition of cancer (glioblastoma) cell growth in comparison with the single conjugates (Gd-NGO/Let–7g and Gd-NGO/EPI) [76].

Tris (bipyridine) ruthenium (II) chloride [Ru(bpy)3] + 2-encapsulated SiNPs, in conjugation with miR-21 molecular beacon (miR-21-MB) and AS1411 aptamer, is a potential cancer theranostic agent (bu-S-AS/MB nanocomposite). miR-21 is involved in a number of pathological conditions, including cardiovascular diseases, pulmonary disorders and cancer [77]. The bu-S-AS/MB nanocomposite was observed to inhibit miR-21 and induce apoptosis by caspase activation. This phenomenon can be simultaneously monitored by virtue of the molecular beacon [78]. A recent study showed a gold NP delivery system for anti-miR-21 to be an excellent platform to target and silence miR-21 in ovarian cancer cells, inhibiting the sphere-forming capacity of tumour-initiating cells. miR-155 is downregulated in ovarian tumour-associated dendritic cells (DCs) and is essential for optimal antigen presentation and activation of T cells by DCs [79]. PEI-based nanocomplexes were used to deliver miR-155 to tumour-associated DCs, which increased the expression of miR-155 *in vitro* and resulted in increased anti-tumour immunity, thus, increased survival of the mice (by 65%). miR-124 was downregulated in ovarian cancer and acted as a tumour suppressor by targeting proteins such as myc while increasing the expression of p27, subsequently leading to cell cycle arrest at G1 phase

because of the loss of phospho-Rb and decreased expression of the myc protein. Transfection of miR-124 in an ovarian cancer cell line reduced the invasive and migration capability of ovarian cancer cells and increased their sensitivity to etoposide by two fold. While miR-124 was restored in ovarian cancer xenograft tumours using 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) NPs, it resulted in a significant decrease in tumour weight alone and in combination with etoposide [80]. Using TCGA, Nishimura et al. identified miR-520d-3p as an independent prognostic marker for EOC, and showed that miR-520d-3p functioned as a tumour suppressor, upstream of the EPHA2 gene. They investigated the effect of dual targeting of EPHA2 with nano-liposomes loaded with miR-520d-3p and EphA2-siRNA which showed synergistic anti-tumour efficiency and greater therapeutic efficacy in vivo than either monotherapy alone [81]. It has been demonstrated that miR-214 represses p53 in ovarian cancer cells and knockdown of miR- 214 increases sensitivity to cisplatin and doxorubicin. Another study showed that TWIST1 (a highly conserved transcription factor) regulates the two pathways IKKb/NF-jB and PTWN/AKT through the expression of the miR199a-2/214 cluster [82]. Yang et al. correspondingly showed miR-214 and miR-199 to be altered in ovarian cancer, and that miR-214 significantly induced cell survival and cisplatin resistance through targeting the PTEN/AKT pathway. Latest, Zheng et al. found that miR-214 disturbs DNA damage responses through downregulation of RNF8 (a protein that plays a key role in DNA damage response) and causes chromosomal instability in ovarian cancer [83].

Conclusion

Many studies now report miRNA dysregulation as a driver of ovarian cancer disease progression. The benefit of miRNA profiling will help us to obtain more accurate diagnoses and even better prognoses. In addition, for clinical use, sensitivity and specificity of miRNA in each disease need to be further investigated. Identifying the miRNAs that are able to affect cancer would be a good start and would aid in improving the targeting and development of new drugs.

Disclosure statement

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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