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Review Article

Anti microRNA in Ovarian Cancer: A Short Review

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Abstract

One of the gynecological cancers with the highest female fatality rate worldwide is ovarian cancer. The extremely high heterogeneity of the illness, its resistance to platinum-based chemotherapy, and the difficulties in performing surgery can be blamed for the modest drop in ovarian cancer mortality. Furthermore, there is no reliable ovarian cancer screening method. Numerous studies, particularly those on micro-RNA, have considerably advanced our understanding of the pathophysiology of ovarian cancer at the molecular level. Short, single-stranded, highly conserved non-coding RNA molecules are known as micro-RNAs (miRNAs) (19 - 25 nucleotides). Numerous studies have found that ovarian cancer and ovarian cancer cell lines exhibit either increased or decreased miRNA expression. The next step is to gather this data and use it to create medicines that target miRNA in order to manage ovarian cancer effectively. This review sought to compile all anti-miRNA investigations that had been done in opposition to miRNA overexpression in ovarian cancer.

Keywords: Ovarian Cancer; Ovarian Malignancy; Ovarian Neoplasm; miRNA; Antagonist miRNA; Anti-miRNA

Introduction

Ovarian cancer has the greatest fatality rate in gynecological cancer. The most prevalent type of ovarian cancer worldwide is epithelial ovarian cancer, which has 5-year survival rate of approximately 25 - 39% in those with advanced-stage disease [1]. Over an extended length of time, this mortality rate did not significantly improve [2]. The combination of surgery and chemotherapy is still the mainstay of management of ovarian cancer. Patients will arrive with advanced stages since there is no adequate screening approach. Advanced-stage ovarian cancer issues include difficult debulking procedures and resistance to conventional chemotherapy (platinum-based chemotherapy). Numerous initiatives have been made to improve medicines, including focused therapy, and biomarkers.

In around 90% of instances, ovarian cancers begin on the ovary's epithelial surface. Four distinct kinds of epithelial ovarian carcinoma can be distinguished morphologically (serous, endometrioid, clear cell, and mucinous). High heterogeneity can be found in epithelial ovarian cancer. Based on the type of protein expression profile that distinguishes or predicts an ovarian cancer's aggressiveness and response to chemotherapy, ovarian tumors can also be divided into high grade and low-grade subtypes. Mutations in the genes PTEN, PIK3CA, KRAS,

BRAF, ERBB2, and ARID1A are indicative of low-grade ovarian cancer. Meanwhile, TP53-related mutations are more prevalent in high-grade ovarian tumors [3,4].

In addition to the significance of these genes that code for proteins, modern genetics revealed that short non-coding RNAs play important roles in cancer, especially ovarian cancer. MicroRNA, also known as miRNA, is a relatively small RNA molecule of 19 - 25 nucleotides, and it was initially identified in 1993. In order to cause the destruction of miRNA or to prevent protein synthesis, microRNA identifies the 3'-untranslated region of the target mRNA [5]. They are expected to control over 60% of human genetics as well as a number of bodily processes, including immune system development, growth, differentiation, metabolism, proliferation, and cell cycle [6]. Numerous research have been published on the expressions of different miRNA profiles in serum, plasma, ascites, and ovarian cancer tissue, resulting in possible biomarkers for diagnosis and prognosis. Additionally, potential processes of different miRNA were examined in light of potential therapeutic applications. Low expression of miRNAs is proposed to be a tumor suppressor gene in the development of ovarian cancer, while high expression of miRNAs on ovarian cancer is suggested to be an oncogene [7,8]. Information about anti-miRNA in ovarian cancer is provided by the current study. Information about anti-miRNA in ovarian cancer is provided by the current study.

Materials and Methods

All anti miRNA research were located through a systematic search of PubMed (Medline) Library. The following search criteria were used to find studies with references in publications published up to June 2022: "ovarian cancer", "ovarian neoplasm", "ovarian carcinoma", "ovarian malignancy", AND "anti-miRNA", "anti miRNA", "anti-microRNA", "anti microRNA", "antagonist miRNA", "antagonist microRNA". There were 384 papers found. Review articles and articles written in languages other than English were not included. Fifty-four documents in all were retrieved for review. There were 30 studies in all that discussed anti-miRNA *in vitro* or *in vivo*.

Biology of miRNA

Micro-RNA (miRNA) was discovered more than 25 years ago in the era of molecular biology. Currently, more than 2000 miRNAs are identified in the human body that regulate one of three genes in the genome [9]. MiRNAs are widely found as small, endogenous, and single stranded RNAs. There are almost 19 - 25 nucleotides that are cleaved from 70 to 100 nucleotide hairpin pre-miRNA precursors [10]. The precursors often form as intramolecular stem-loop structures. The mature miRNA does not contain an open reading frame. MiRNA genes reside throughout the genome, and many of them are codeless genes. These genes may be present in a single miRNA gene or in a cluster of miRNA genes. Location of miRNAs gene can be between two genes (intergenic) or within a gene (intronic). The intronic miRNAs may be placed between two exons (miRtron) or overlapping an exon. Sometimes, they may exist in an intron of non-coding genes (mixed) [11]. MiRNAs interacted with target mRNAs can induce mRNA degradation or block its translation. In most cases, the miRNA will interact with the 3' untranslated region (3' UTR) of the mRNA. However, their interactions with other sites, such as 5' UTR, coding sequences, and gene promoters have also been reported [12].

RNA polymerase II mediates the transcription of miRNAs and creates primary-miRNAs (Figure 1). They require two endonucleation processes before becoming mature and active. The first step in breaking miRNA involves transcription, which is assisted by the nuclear RNase II microprocessor complex DROSHA and DGCR8. The primary RNAs will be chopped, added to, and altered in accordance with the mRNA code to create intermediates that resemble 60 - 70 nucleotide hairpins (premature miRNAs or pre-miRNA). The second procedure involves exportin 5 (EXP5) moving the premature miRNAs into the cytoplasm. The RNase III DICER complex enzyme, which destroys the curved portion of the protein to generate mature miRNAs, cleaves the pre-miRNAs in the second step. Depending on the type of miRNA, the results of endonucleation range from 19 to 25 nucleotides. DICER processing also involves the transactivating response RNA binding protein and other regulatory elements (TRBP). The protein controls the DICER enzyme and manufacture of miRNA species via the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway [9,13-15].

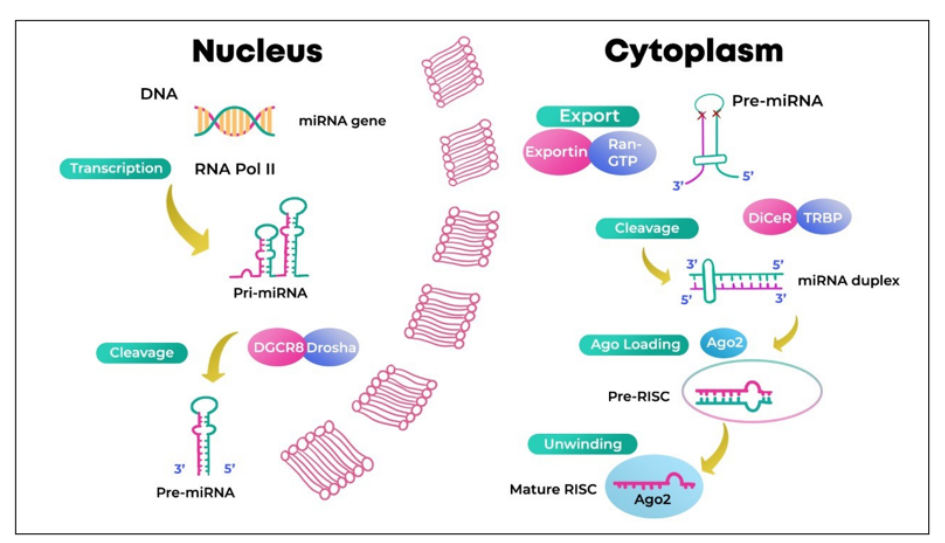

Figure 1: *Biogenesis of miRNA. Primary miRNA is first translated by RNA polymerase II, and then it is transformed into pre-miRNA inside the nucleus by the enzyme DROSHA. With the aid of exportin 5, pre-miRNA leaves the nucleus (EXP5). Advanced method using RISC and dicer enzymes, with breakdown and degradation based on the target mRNA transcript.*

Small molecule RNA duplex binds to Argonaute protein (AGO1, AGO2, AGO3, or AGO4) and form a complex mature RISC which eventually binds to the 3'-untranslated region of the target mRNA (3'UTR). The facilitated binding can direct the complex into perfect or imperfect base pairing. If the complementary bind of miRNA and 3'UTR is complete, the miRNA target will be degraded. On the other hand, the incomplete binding will hamper the translation process. These process happened in the processing bodies (P-bodies) placed in the cytoplasm focus [14].

MicroRNA and ovarian cancer

Changes in miRNA expression have an impact on gene expression. Any malignancy, particularly ovarian cancer with its intricate pathways, can have altered microRNA levels. MiRNAs that are overexpressed function as oncogenes by reducing the regulation of tumor-suppressor genes, regulating cell differentiation, or controlling apoptosis. Amplification, the dysregulation of transcription factors in promoter genes, is impacted by this excessive expression. MiRNA may diminish regulation through gene transcription factor reduction, epigenetic stoppage, or deletion as a tumor suppressant [16,17]. By contrasting the levels of miRNA expression in healthy tissue versus ovarian cancer, significant variations can be seen in a few miRNAs.

MicroRNA as oncogene in ovarian cancer

Genes involved in cell proliferation and essential for maintaining normal life activity are referred to as proto-oncogenes. Tumor development can result from abnormal cell behavior brought on by abnormal structures or unchecked proto-oncogene expression. Certain miRNAs have highly regulated levels of expression in tumor tissue, which is indicative of proto-oncogene properties. Additionally, increased regulation of their expression may lead to the growth of malignant cells. According to research using a gene chip on ovarian cancer tissue, the expression of miR-200c, miR-141, and miR-155 was noticeably higher than that of normal ovaries [10]. MicroRNA-200a

and miR-141 have been reported to target p38α MAPK whose role is decreasing cell capacity to develop tumor via regulating cell proliferation, survival and stress response [18,19]. Ectopic expression of miR200a was reported to sensitize OVCAR-3 ovarian cancer cell line to paclitaxel [20]. MiR-200a-3p was shown to be more highly expressed in ovarian cancer tissue and cell lines in one study, and it was found to be substantially correlated with tumor size, tumor metastasis, and TNM stage. Additional research in the form of functional tests revealed that miR-200a-3p binds to the 3'-UTR of PCDH9 and inhibits its expression in ovarian cancer cells. MiR-200a-3p expression was strongly inversely linked with PCDH9 in ovarian cancer tissue [21].

Additionally, ovarian cancer tissue was shown to express miR-141 higher than normal ovary. Ovarian cancer cells undergo peritoneal metastasis, tumor development, and cell proliferation when miR-141 expression is elevated. The Kruppel AP-2rep (KLF12) protein was the target of miR-141, and ovarian cancer cells showed a reduction in this protein. The inhibition of sp1-mediated survivin transcription, which blocks intrinsic apoptosis pathways, causes improvements in KLF12 proteins in cells expressing miR-141 to significantly weaken anoikis resistance in ovarian cancer cells. Tests using immunohistochemistry (IHC) and in situ hybridization (ISH) demonstrate that miRNA-141 expression is strongly inversely connected with KLF12 expression in advanced ovarian cancer [22].

Another miR-200 family member, miR-429, has been shown to transform mesenchymal epithelial cells into epithelial cells after being transfected into cell lines. At the mRNA level, changes were also made to the epithelial-mesenchymal transition (EMT)-related genes ZEB1, ZEB2, E-cadherin, N-cadherin, fibronectin 1 (FN1), and vimentin. 296 genes were dramatically downregulated in this study's microarray detection, including the mesenchymal cell markers ZEB1 and Versican (VCAN). Tetraspanin 13 (TSPAN13), Caveolin 2 (CAV2), Desmoplakin (DSP), and epithelial cell adhesion molecule (EPCAM/the epithelial cell adhesion molecule) were among the 373 genes whose expression was considerably upregulated. Therefore, it can be said that miR-429 plays a crucial part in controlling EMT in ovarian cancer [23,24].

Epithelial ovarian cancer has increased miR-630 expression when compared to healthy ovarian tissue. The proliferation and migration of SKOV3 epithelial ovarian cancer cells are encouraged by the elevated expression of miR-630. The protein Krüppel-like factor 6 (KLF6) was anticipated to be a target for miR-630, according to the study. The same *in vivo* investigation established that increased miR-630 expression promotes the development of ovarian cancer [25].

miRNA as tumor suppressor gene in ovarian cancer

A gene called a tumor suppressor gene is involved in preventing the growth of tumors. Products from tumor suppressor genes can prevent cell division, encourage cell differentiation, and/or prevent cell migration. Certain miRNAs significantly decreased and exhibited tumor suppressor gene characteristics. Let-7 family that acts as a tumor suppressor gene has been reported by several studies in malignancies such as breast, lung, stomach, colon, and ovarian cancers. It was reported that the target genes of let-7 family were the early embryonic genes HMGA2 and IMP-1 as well as oncogenic NRAS [22,25]. High levels of ovarian cancer have been linked to overexpression of the nuclear binder HMGA2, which belongs to the high mobility group of proteins. Additionally, HMGA2 controls how cells differentiate and proliferate. According to another study, the survival rates of ovarian cancer patients who exhibit let-7 downregulation and HMGA2 overexpression had lower survival rates [26,27].

Cyclins, protein kinases, and their inhibitors, among others, operate as growth factors and suppressors to slow down or stop the progression of the cell cycle. Understanding the methods by which tumor suppressants of miRNAs to control cell proliferation and cell cycle developmental pathways in ovarian cancer has become the focus of an expanding corpus of study over time. A few miRNAs that have kinases that depend on cyclin (CDK), CDK4/6 and CDK14 as their targets are miR-506, miR-211, miR-542-3p, miR-590-3p, and miR-23b. By triggering a number of downstream pathways, these tumor suppressive miRNAs can prevent cancer cells from multiplying and moving through various stages of the cell cycle [26-32].

Anti-miRNA and ovarian cancer

Mechanisms to regulate miRNA activity can be carried out by restoring miRNA expression of tumor suppressor genes or by blocking the activity of oncogenic miRNAs. However, these two strategies can also be combined. The restoration of miRNA expression of tumor suppressor genes is accomplished by providing double-stranded chemically synthesized miRNA mimics or using viral vectors to increase miRNA expression. MiRNA mimics are synthesized to target a single mRNA or multiple mRNAs. The miRNA overexpression using viral vectors is carried out by integrating a vector system containing short hairpin RNAs (shRNAs) which were activated by Pol III promoters. Meanwhile, miRNA loss-of-function modulation system can be carried out by applying miRNA sponge, miRNA-masking oligonucleotide antisense, or antisense oligonucleotide targeting miRNA [33,34]. Up until September 2022, studies on anti-miRNA were done, as shown in table 1.

No.	miRNA	Anti-miRNA	Pathway	Ref.
1.	miR-21	1. Anti miR-21 2. Anti miR-21 with Fol-miR21-NCs 3. Anti miR-21 with folate-lipid-PLGA hybrid-polymer nanoparticle 4. Anti miR-21 with PEG2k-CMPEI-ss 5. Anti miR-21 with biodegradable porous silicone nanoparticles (pSINPs) 6. Anti miR-21 with AS1411 anti-nucleolin aptamer-decorated PEGylated poly-(lactic-*co*-glycolic acid) nanoparticles	Antisense oligonucleotide targeting miRNAs	[35,37-39,41,53,54
2.	miR-221	Anti miR-221	Antisense oligonucleotide targeting miRNAs	[55]
3.	miR-214	Anti miR-214 loaded in antisense MNA-loaded nanoparticles of star shaped-glucose-core	Antisense oligonucleotide targeting miRNAs	[48]
4.	miR-429	Anti miR-429	Antisense oligonucleotide targeting miRNAs	[49]
5.	miR-324-5p	Anti miR-324-5p in chitosan	Antisense oligonucleotide targeting miRNAs	[56]
6.	miR-204-5p	Anti miR-204-5p with Scavenger receptor class B type 1 (SCARB1)	Antisense oligonucleotide targeting miRNAs	[52]
7.	miR-383	Anti miR-383 inhibitor (20-O-methyl modification) with lentivirus	Antisense oligonucleotide targeting miRNAs	[57]
8.	miR-23a	Anti miR-23a	Antisense oligonucleotide targeting miRNAs	[50]

9.	miR-14U miR-4350-10G-GA miR-4350-HAA-GCU	1. MiRNA (miR-14U) was created by introducing a mutation in the nt 14 counting from the 5' end of anti-sense RNA 2. MiR-4350-10GGA and miR-4350-HAAGCU were created by introducing either loop-forming nucleotides in position 10 or in position 11	Synthetic miRNA	[58]
10.	miR-21	Circ9119	Sponge of miR-21	[53]
11.	miR-28	CircAHNAK	Sponge of miR-28	[59]
11.	miR-431-5p	LINC01132	Sponge of miR-431-5p	[60,61]
12.	miR-183-5p	Pc-DNA-LEMD1-AS1 (LEMD1 antisense-1)	Sponge of miR-183-5p	[62]
13.	miR-525-5p	MAGI2-AS3	Sponge of miR-525-5p	[63]
14.	miR-30e-3p	MEG3 and LAMA4	Sponge of miR-30e-3p	[64]
15.	miR-138-5p	HOTAIR	Sponge of miR-138-5p	[65]
16.	miR-15b-5p	LncRNA TTN-AS1	Sponge of miR15b-5p	[66]
17.	miR-654-5p	Long non-coding RNA UCA1	Sponge of miR-654-5p	[67]
18.	miR-1228	Mimic circular RNA-100395	Sponge of miR-1228	[68]
19.	miR-421	Anisomycin	Sponge of miR-421	[69]
20.	miR-25	Physcion 8-O-β-glucopyranoside	Sponge of miR-25	[70]
21.	miR-340-5p	LncRNA HAND2-AS1	Sponge of miR-340-5p	[71]
22.	miR-331-3p	Anti Has_circ_0004712	Sponge of miR-331-3p	[72]

Table 1: *Anti-miRNA in the ovarian cancer studies.*

Studies targeting miRNA on ovarian cancer have been conducted frequently using anti-miRNA or miRNA sponge. When a miRNA or a family of miRNAs is knocked down using a miRNA sponge, this can have unfavorable consequences on all target genes as well as the targeted miRNAs. On the other side, the most often used method to reduce miRNA overexpression is to use antisense oligonucleotide miRNA. Antisense oligonucleotides promote the RNase-dependent degradation of the target RNA in order to inhibit defective miRNA. By utilizing antisense oligonucleotides to target overexpressed miRNAs, this technique tries to regulate the post-transcriptional gene. Identification of highly effective anti-miRNAs or antisense oligonucleotides is necessary to improve them through chemical modification [33].

The most common miRNA investigated with either antisense oligonucleotide/anti-miR-21 or a sponge of miR-21 was miRNA-21 (Table 1). Anti-miR-21 was used to inhibit overexpressed miR-21, which attenuated cancer cell death. The Cancer Genome Atlas revealed that overexpressed miR-21 and a shorter progression free survival were linked with advanced ovarian cancer. This research showed that inhibiting miR-21 increased the expression of the tumor suppressor PDC4 and triggered apoptosis [35,36]. The following investigations looked for the best anti-miR-21 vehicle. In a study using the A2780 R cells, AS1411 antinucleolin aptamer-decorated PEGylated polylactic-co-glycolic acid (PLGA) nanoparticles were used and reported to increase cancer cell mortality [37]. Using an ultrasound and microbubble-mediated (US-MB) delivery method, another vehicle was created by encasing anti miR-21 in folate-lipid-PLGA hybrid nanopolymers. According to the study, co-delivery of SIK2 siRNA and anti miR-21 through the use of US-MB considerably increased the sensitivity of ovarian cancer cells to the drug paclitaxel and was successful in treating ovarian cancer cells in separate studies [38]. Various methods of anti-miR-21 delivery system have also been reported, including the use of porous silicon nanoparticles (pSNIPs), a series of branched polyethylenimine (PEI) modifications, including PEGylation (PEG2k-PEI) for steric shielding, redox-sensitive crosslinking to

create PEG2k-PEI-ss nanogels, followed by carbomethylation (PEG2k-CMEI These trials provided information on the efficient delivery of anti-miR-21 both with and without conventional chemotherapy [39-41].

According to a study using anti-miR-221 transfection in SKOV3 cancer cells, miR-221 dysregulation can greatly enhance the production of the protein Bcl2 modifying factor (BMF), which in turn significantly decreases cell proliferation and increases the likelihood of cell apoptosis. As is widely known, BMF's primary function is to trigger cell death by binding to the proteins Bcl2, Bcl-xL, and Bcl-w, which are involved in B-cell lymphoma anti-apoptotic factor (Bcl2). In a variety of malignancies, including lymphoma, breast cancer, and colon cancer, BMF functions as a tumor suppressor gene [42-44].

Ovarian cancer which is very heterogeneous in nature raises the problem of cisplatin chemotherapy resistance. Numerous investigations have revealed that there is a high association between chemotherapy resistance and miR-214 expression in pancreatic cancer and gastric cancer in addition to ovarian cancer [45]. It has been well investigated and confirmed that increased miR-214 expression is linked to enhanced chemo-resistance in a number of malignancies. In advanced ovarian cancer patients, miR-214 expression was reported to increase 8.23 times. MiR-214 can control PTEN by binding to its 3′-UTR, which represses the translation of PTEN and activates the Akt signaling cascade. MiR-214 can prolong the survival of cancer cells and retain their capacity to tolerate cisplatin by activating the AKT pathway [46]. Research Wang., *et al*. showed that exosomes carrying anti-miR-214 could induce gastric cancer cell re-sensitization *in vitro* and *in vivo* [47]. In ovarian cancer cells A2780 R, the targeted inhibition of miR-214 using developed nanoparticles containing locked nucleic acid LNA decreases drug-resistant properties of cancer cells [48].

A study revealed that exosomal miR-429 targets the calcium-sensing receptor (CASR)/STAT3 pathway *in vitro* and *in vivo* to promote proliferation and treatment resistance in the A2780 cell line. By targeting CASR through NF-B-supported mechanisms, miR-429 exosomes function as important regulators of chemoresistance and the malignant phenotype of epithelial-type ovarian cancer. It was proposed that internalized SKOV3-derived exosomes to transmit anti-miR-429 and NF-B inhibitors improved anti-miRNA transfer and lowering miR-429 expression [49].

By suppressing the expression of miR-23a, another study attempted to ascertain the modifications in sensitivity and initial mechanism of ovarian cancer cells to chemotherapeutic drug resistance. After giving anti-miR-23a and platinum to cell lines A2780, the amount of cell proliferation inhibition was noticeably elevated. The rate of apoptosis increased, the cells appeared to stop dividing, and they were in the G0/G1 phase [50]. Through the suppression of P-gp protein production, miR-23a expression can greatly improve cell susceptibility to cisplatin. On chromosome 7, the tumor multi-drug resistance gene 1 (MDR1) produces the protein known as P-gp. The cytomembrane contains the ATP-binding P-gp protein, which functions as a pump to expel chemotherapeutic drugs from the cell. Consequently, this protein can prevent the buildup of chemotherapeutic drugs and result in a resistance mechanism for classical resistance [51].

Administration of anti-angiogenic drugs, whose effects are based on blocking the vascular endothelial growth factor pathway, is another strategy for treating ovarian cancer. This strategy is typically used in conjunction with other therapeutic strategies. MiR-204-5p can, *in vitro* and *in vivo*, enhance angiogenesis in ovarian cancers via thrombospondin1/THBS1, according to one research of miRNA profiling from patient data sets. Reconstituted High-density Lipoprotein-Nanoparticles (rHDL-NPs) harboring anti-miR-204-5p can have anti-angiogenesis effects through interacting with scavenger receptor class B type 1 (SCARB1) [52].

Ovarian cancer exhibits higher levels of miR-383 expression than glioma, medulloblastoma, testical embryonal carcinoma, or gastric cancer, which exhibit lower levels [73-76]. MiR-383 controls how much estradiol human ovarian granulosa cells secrete. Inhibition or administration of anti-miR-383 exhibited a tumor-suppressing impact that prevented the growth of ovarian cancer cells, according to research by Liu J., *et al*. This suppression procedure is associated with CASP2/caspase2, which functions as a protein maker that triggers ovarian cancer cell death (and is a target gene for miR-383) [77].

Despite the fact that numerous anti-miRNA research has been carried out, only a few anti-miR has advanced to a clinical trial. The first anti-miRNA oligonucleotide that targets miR-122 has undergone clinical testing and has demonstrated encouraging results as a therapeutic agent in the treatment of chronic HCV infection [78-80]. Learning from HCV infection with anti-miRNA, an *in vivo* study suggested that miR-122 promotes RV-induced lung disease via suppression of its target SOCS1. The potential use of anti-miR-122 oligonucleotides was highlighted by the finding that higher miR-122 expression was linked to lower clinical outcomes [81]. Another clinical trial using anti-miRNA showed in vascular disease and wound healing. Suppression of miR-92a by antisense oligonucleotide MRG-110 increased vascularization after myocardial infarction and blood circulation after hind limb ischemia in human [82].

Conclusion

Patients with ovarian cancer require comprehensive care that includes both chemotherapy and surgical procedures. There are several difficulties, ranging from high treatment resistance because of the disease's heterogeneity to a delayed diagnosis because there is no appropriate screening approach. The development of miRNAs as therapeutic targets or biomarkers, however, faces numerous difficulties. These difficulties include identifying the best miRNAs to target therapeutically, sample techniques, and genetic background. The development of anti-miRNA as a targeted therapeutic is still ongoing. Only 4% of all miRNA research have focused on the involvement of miRNAs in the targeted therapy of ovarian cancer. The objective of this review is to compile all anti-miRNA studies that have been published up to 2022. Potential targeted treatments for ovarian cancer include research utilizing anti-miRNA oligonucleotides, synthetic miRNAs, or other miRNA oncogenic activity inhibitors.

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Volume 12 Issue 2 February 2023