E.T. Mingazheva, Yu. Yu. Fedorova, A.Kh. Nurgalieva, Ya.V. Valova, E.A. Andreeva, A.V. Sagitova, R.R. Faiskhanova, D.D. Sakaeva, E.K. Khusnutdinova, D.S. Prokofyeva

THE ROLE OF MICRORNAS IN THE PATHOGENESIS OF OVARIAN CANCER

DOI 10.25789/YMJ.2024.85.21
UDC 616-006:575.1

This review collects and summarizes the literature data accumulated over the past few years on the participation of microRNAs in the pathogenesis, progression and metastasis of ovarian cancer, as well as their role in the emergence of multidrug resistance, and considers their possibility of use as prognostic and diagnostic biomarkers.

Keywords: ovarian cancer, microRNA, oncogenetics, drug resistance and sensitivity, methylation.

Introduction. Ovarian cancer (OC) is the most aggressive tumor among malignant neoplasms of the female reproductive system and occupies a leading place in mortality among gynecological oncological diseases. According to the latest global statistics, the number of new cases of the disease in 2020 exceeded more than 300 thousand and more than 207 thousand women died from this pathology [20]. The high mortality rate of ovarian cancer is primarily due to its nonspecific symptoms, which usually appear as the disease progresses, as well as the lack of effective screening methods to detect it in the early stages.

Currently, clinical treatment of OC is based on cytoreductive surgery to reduce tumor volume and subsequent combination chemotherapy using cisplatin and paclitaxel. However, despite an initial good response to therapy, most patients progress to disease relapse and eventually develop chemotherapy-resistant pathology. In addition, ovarian cancer has a high metastatic and invasive potential, and metastasis increases multidrug resistance and sharply reduces patient survival [22].

One of the most outstanding discoveries in biology of the last decade should be considered the discovery of a systemic level of regulation of gene activity using small non-coding molecules - microRNAs [1].

This review collects and summarizes the literature data accumulated over the past few years on the participation of microRNAs in the pathogenesis, progression and metastasis of ovarian cancer, as well as their role in the emergence of multidrug resistance, and considers their possibility of use as prognostic and diagnostic biomarkers.

MicroRNA – formation, signaling pathways and target genes. MicroRNAs (miRNAs) are a type of small non-coding RNAs, approximately 19–25 nucleotides in length, that are involved in the regulation of gene expression, typically by inhibiting translation and attenuating the stability of messenger RNAs (mRNAs). The first works describing microRNAs were published in 1993 by a group of researchers led by V. Ambros and G. Ruvkun, who studied the mechanisms of regulation of development of the nematode Caenorhabditis elegans [28]. To date, about 1917 precursors and 2654 mature human microRNAs have been identified, their description is provided in the microRNA database (miRbase.org). MicroRNA genes are evolutionarily conserved and distributed throughout the human genome. A small part of microRNAs (about 10%) is located in the introns of coding genes. About half of all microRNAs are found within or adjacent to sites of chromosome fragility, in areas of loss of heterozygosity, or in regions of genome amplification in tumors. This type of non-coding RNA regulates the expression of more than 60% of human genes at the transcriptional and post-transcriptional levels [51].

Transcription of microRNA genes is carried out by RNA polymerase II with the formation of a primary transcript - pri-microRNA, about 1000 nucleotides in length. Primary transcripts form several double-stranded regions - hairpins, which are then cut into individual molecules of 60 to 75 nucleotides in length (pre-microRNA) using a nuclear complex formed by Drosha RNase III and the Pasha protein (from partner of Drosha, DGCR8), which recognizes double-stranded RNA . Pre-microRNA molecules are transported by the exportin 5/Ran GTPase complex into the cytoplasm, where further microRNA maturation occurs. In the cytoplasm, pre-microRNA is cut by RNase III Dicer into duplex RNA 18–25 nucleotides long (mature microRNA). Mature microRNA binds to the Ago2 protein from the Argonaute family and forms the so-called RISC complex (miRNA-induced silencing complex), which provides the main function of microRNA - suppression of gene expression. The choice of target gene is

MINGAZHEVA Elvira Tagirovna – Senior Researcher of laboratory population and medical genetics, PhD in Biology, e-mail: Elvira.F91@mail.ru; **FEDOROVA Yulia Yurievna** – Senior Researcher of laboratory population and medical genetics, PhD in Biology, e-mail: fedorova-y@yandex.ru; **NURGALIEVA Alfiya Khamatyanovna** – Senior Researcher at the Laboratory of Population and Medical Genetics, Ufa University of Science and Technology, PhD in Biology, e-mail: alfiyakh83@gmail.com; **VALOVA Yana Valeryevna** – Junior Researcher of laboratory population and medical genetics Ufa University of Science and Technology, e-mail: q.juk@ya.ru; **ANDREEVA Ekaterina Anatolyevna** – PhD student of Ufa University of Science and Technology, e-mail: ekaterinabiology@yandex.ru; **SAGITOVA Alina Valerievna** – Master Department of Medical Genetics and Fundamental Medicine of Ufa University of Science and Technology, e-mail: sagitova.lina2014@yandex.ru; **FAISHKHANOVA Rania Razyapovna** – oncologist of the State Autonomous Institution of the Ministry of Health of the Republic of Bashkortostan "Republican Clinical Oncology Dispensary", Candidate of Medical Sciences, e-mail: rancho111@mail.ru; **SAKAEVA Dina Damirovna** – Department of Pharmacology with a Course of Clinical Pharmacology, Bashkir State Medical University, Professor, Doctor of Medical Sciences, e-mail: ddsakaeva@bashgmu.ru; **KHUSNUTDINOVA Elza Kamilevna** – Professor, Doctor of Sciences in Biology, Academician of the Academy of Sciences of the Republic Bashkortostan, Corresponding member of the Russian Academy of Eductaion, Director of the Institute of Biochemistry and Genetics – Subdivision of the Ufa Federal Research Centre of the Russian Academy of Sciences; e-mail: elzakh@mail.ru; **PROKOFYEVA Darya Simonovna** – head of laboratory population and medical genetics, PhD in Biology, e-mail: dager-glaid@yandex.ru

determined by the complementarity of the key sequence (seed sequence) of the microRNA and the mRNA sequence (binding sites for microRNA), which are most often located in the 3' untranslated region (Figure) [1,38].

It has been established that microRNAs are actively involved in the regulation of a wide variety of biological processes, including cell proliferation and differentiation, apoptosis, angiogenesis, inflammation, etc. The effects of microRNAs cover such key processes for tumor growth as migration, invasion and metastasis, epithelial-mesenchymal transition (EMT)) [3].

The first data on the involvement of microRNAs in the development of malignant neoplasms were obtained in 2002 by G.A. Calin et al. [11]. Over the next 13 years, various scientific groups have carried out many studies on the role of microRNAs in carcinogenesis. An association of specific microRNA expression profiles with the TNM stage of the disease, histological type of tumor, molecular genetic events in tumor cells, and response to therapy has been shown [2, 37, 57,58].

The first study of changes in the level of microRNA expression in OC was performed in 2007 in the laboratory of S.M. Croce on 69 tissue samples from patients with ovarian cancer and 15 normal tissue samples. A significant increase in the expression levels of miR-200a, miR-141, miR-200c and miR-200b and a decrease in the levels of miR-199A, miR-140, miR-145 and miR-125b1 were found. In addition, the authors of the work were able not only to differentiate ovarian cancer samples from normal ovarian tissues, but also to identify some of its histological subtypes. For example, miR-21, miR-203 and miR-205 were overexpressed only in tumor samples of the endometrioid histotype OC [23,40]. A number of other studies have also shown that different OC histotypes demonstrate differential expression of specific microRNAs. Thus, miR-509-3-5p, miR-509-5p, 509-3p and miR-510 were significantly overexpressed in clear cell ovarian carcinoma samples compared to high-grade serous OC, while increased expression of miR-200c- 3p has been associated with poor survival prognosis in patients with high-grade serous ovarian cancer [45,46]. In the work of Agostini et al. It was found that the expression of miR-192, miR-194 and miR-215 was significantly increased in ovarian carcinomas of the mucinous subtype, but was suppressed in other histotypes and sex cord stromal tumors [6].

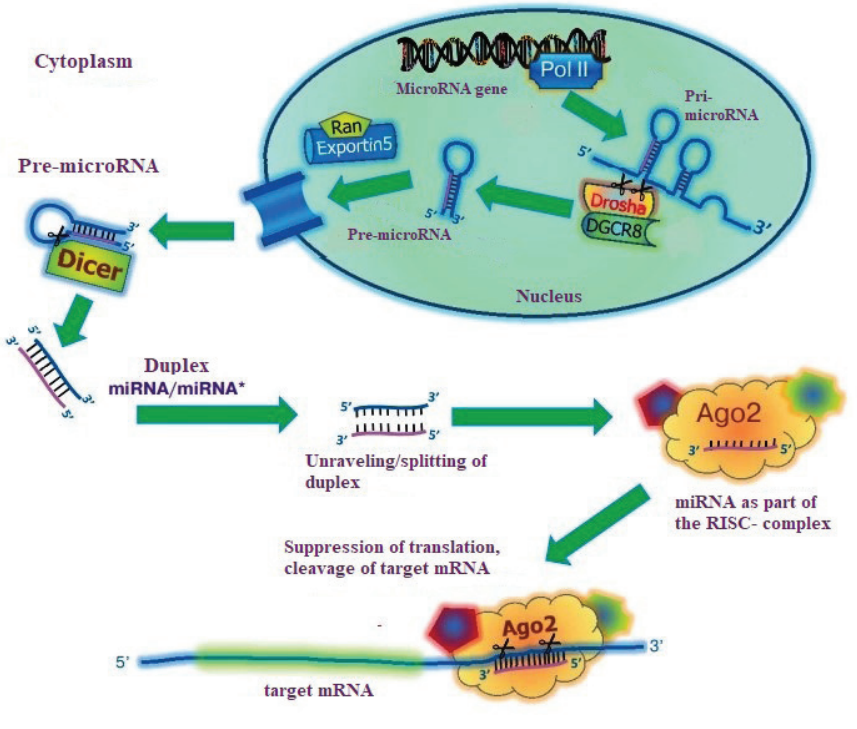
Depending on which gene expression is suppressed by microRNAs, they can function as tumor suppressors or oncogenes. The expression of oncogenic miRNAs is typically upregulated in most tumor types, promoting malignant transformation and cancer progression. For example, in the work of Wang Z. et al. Using a comprehensive meta-analysis approach, it was demonstrated that miR-27a may promote the progression of ovarian cancer through the regulation of one of the transcription factors, the FOXO1 protein [49]. In an experiment on human ovarian cancer cell lines HO8910 and OVCAR-3, Hu Y. et al. showed that miR-934 promoted tumor cell proliferation through inhibition of the metastasis suppressor BRMS1L [21].

Tumor suppressor microRNAs can suppress cancer development by inhibiting oncogenes. The main effects of suppressor microRNAs are inhibition of proliferation, migration and invasion, stimulation of apoptosis, suppression or reversal of EMT, as well as overcoming or reducing multidrug resistance, in particular resistance to taxanes and platinum drugs [3]. Similar to protein-coding tumor suppressor genes, such microRNAs are often deleted, mutated, or methylated in various human tumors.

Thus, Li et al. showed that the expression of miR-542-3p was significantly reduced in tissues and cell lines of epithelial ovarian cancer. Further functional assays showed that overexpression of miR-542-3p suppressed tumor cell proliferation, migration and invasion in vitro, whereas knockdown of miR-542-3p promoted tumor cell proliferation and invasion. In vivo analysis also showed that overexpression of miR-542-3p significantly attenuated tumor growth [29]. In a similar study, Jia et al. reported that upregulation of miR-34 induces autophagy and apoptosis of tumor cells, regulates tumor proliferation, and inhibits cell invasion by suppressing Notch1 protein expression [24].

Other representatives of suppressor microRNAs include the let-7 family. MicroRNAs of this family inhibit the growth and invasion of tumor cells by suppressing the expression of proto-oncogene-encoded proteins KRAS, HRAS, c-MYC and HMGA-2, as well as cell cycle regulators such as CDC25, CDK6 and cyclins A, D1, D2 and D3. A decrease in the expression of let-7e, let-7f, let-7d, let-7c, let-7i, let-7a, let-7b in the tumor and let-7f, let-7d in ovarian cancer cell lines was detected [54].

Depending on the cellular and tissue environment, some microRNAs can suppress or promote malignant cell transformation [7]. The most striking example is the miR-200 family of microRNAs. MicroRNAs of this family are responsible for regulating the EMT process by suppressing the expression of E-cadherin transcription inhibitors ZEB1 and ZEB2 [8]. In turn, ZEB may reduce transcription of the miR-200 family. Presumably, in the



MicroRNA biogenesis [1]

early stages of ovarian cancer development, a mesenchymal-epithelial transition occurs, increasing the expression of microRNAs of this family, and with the spread of metastases, EMT occurs, reducing it [2,19]. The miR-200 family has also been reported to inhibit blood vessel formation by directly or indirectly affecting interleukin-8 secreted by tumor epithelial cells and the chemokine CXCL-1. Transfection of microRNAs of the miR-200 family into the epithelium showed a significant reduction in tumor cell metastasis and angiogenesis, as well as normalization of blood vessels [7].

Recent work by Choi et al., examining plasma and serum samples from 118 patients with epithelial ovarian cancer (EOC) and 96 healthy controls, found increased levels of miR-200a, miR-200b and miR-200c in patients compared to controls. . Researchers also found differences in miR-200 expression levels associated with subtypes, with serous and mucinous tumors showing increased levels of miR-200b and miR-200c, and clear cell and endometrioid tumors having increased expression of miR-429 [17].

The expression level of miR-200 family microRNAs may be a prognostic factor for survival. In particular, increased expression of miR-200a and miR-200b in serum and tissue correlates with lower overall and disease-free survival [10,55].

For the microRNA cluster miR-214-199-a2, both overexpression in ovarian cancer and a decrease in the level of synthesis compared to normal have been described. Thus, in a study by Liu et al., it was shown that SKOV3 cells transfected with a miR-214 mimic showed significantly increased viability and proliferation, as well as a noticeable decrease in the rate of apoptosis. In addition, PTEN protein expression was decreased and PIP3, p-Akt, and p-GSK-3β protein expression was significantly increased. The authors of the study concluded that miR-214 can activate the PI3K/Akt signaling pathway by suppressing PTEN, which can promote proliferation and inhibit apoptosis of OC cells [34]. Another study reported that overexpression of miR-214 suppresses cell proliferation and induces apoptosis by negatively controlling the semaphorin-4D gene in tumor cells [35]. However, miR-214 belongs to microRNAs that are found in exosomes and circulate in the blood, and therefore it can be used for non-invasive diagnostics.

Thus, to date, extensive information has been accumulated on the effect of microRNAs on the progression of ovarian cancer. It is known that microRNA expression profiles are specific for both different types of histologically normal and tumor tissues. However, the results of research to date are quite contradictory, which undoubtedly requires a more detailed study of microRNA expression for each specific tumor type, which will ultimately contribute to the understanding of the pathogenesis of malignant neoplasms, as well as the development of sets of molecular markers for the prognosis and diagnosis of cancer. diseases based on microRNA analysis.

2. Drug resistance and sensitivity in the treatment of malignant neoplasms: disruption of microRNA genes. Chemoresistance remains a major barrier to effective treatment of patients with ovarian cancer, and recently, increasing evidence suggests that microRNAs are involved in the development of drug resistance [18, 25, 50]. Studies of the role of microRNAs in the formation of chemoresistance in ovarian cancer are based on comparing the levels of microRNAs in cells of insensitive and sensitive tumors or cell lines, identifying differentially expressed microRNAs and their targets. Due to the wide heterogeneity of the molecular genetic characteristics of tumor cells within one histological type and the dual role of individual microRNAs in carcinogenesis, researchers are obtaining a large number of potentially significant microRNAs, including conflicting results.

Members of the ABC transporter family play an important role in the development of multidrug resistance (MDR). Yang et al. It has been shown that suppression of miR-130a can inhibit MDR1 gene mRNA expression and overcome treatment resistance in the cisplatin-insensitive ovarian cancer cell line SKOV3/CIS [53]. Similar results were obtained in the work of Li et al., who found that miR-130a and miR-374a mimetics reduce the sensitivity of A2780 cells to cisplatin, and vice versa; their inhibitors can resensitize cells of the cisplatin-resistant A2780/DDP line. In addition, the authors of the study noted that overexpression of miR-130a can increase the levels of MDR1 gene mRNA in A2780 and A2780/DDP cells, while knockdown of miR-130a can inhibit the expression of the MDR1 gene and activate the PTEN protein [30].

Another study showed that miR-199a significantly increased the chemosensitivity of CD44+/CD117+ ovarian cancer stem cells to cisplatin, pacitaxel, and adriamycin, and decreased mRNA expression of the multidrug resistance gene ABCG2 compared to cells transfected or untransfected with miR-199a mutants [16]. In a study by Zong et al., transfection of miR-130b into the OC cell line A2780 and paclitaxel-resistant A2780/Taxol cells resulted in suppression of MDR1 protein and increased sensitivity to paclitaxel and cisplatin in both cells [59]. The same results were obtained for miR-490-3P, miR-133b, miR-873 and miR-186 in the same ovarian cancer cell lines [12, 13, 51, 41,42].

In addition to drug transporters, a number of genes involved in the regulation of apoptosis may be potential targets of microRNAs in the regulation of chemosensitivity in human cancer. For example, it was found that microRNAs miR-130a, miR-137 and miR-142-5p are able to regulate the sensitivity of OC cells to cisplatin by influencing the expression of XIAP (X-linked inhibitor of apoptosis) [14, 31, 32,56]. A study by Kong et al found that miR-125b promotes cisplatin resistance by suppressing Bcl-2 expression in the resistant C13* cell line [26]. Decreased serum miR-125b levels were also significantly associated with increased chemoresistance in patients in a study by Chen et al [15]. Additionally, a study by Parayath et al showed that miR-125b encapsulated in hyaluronic acid-based nanoparticles (HA-PEI-miR-125b) in combination with intraperitoneal paclitaxel could enhance the antitumor efficacy of paclitaxel in patients with ovarian cancer [39].

The most frequently studied miRNAs that are associated with chemotherapy sensitivity are the let-7 and miR-200 families. Lu et al. observed that let-7a expression was significantly lower in ovarian cancer patients who were sensitive to platinum and paclitaxel compared with those who were resistant to these drugs. In addition, overexpression of this miRNA may enhance the effect of platinum alone, but may negatively affect the prognosis of combination treatment (for example, carboplatin + paclitaxel first line) [37]. In the work of Wang et al., a novel targeted hyaluronic acid-modified nanosystem using gold nanorods coated with functionalized mesoporous silica nanoparticles was developed for the combined delivery of paclitaxel and let-7a microRNA to overcome MDR in ovarian cancer. The authors of the study showed that this nanosistema can stably combine and transport paclitaxel and microRNA, and also specifically bind to the CD44 receptor, which is highly expressed in SKOV3 cells and chemotherapy-resistant SKOV3 TR cells, ensuring effective uptake by cells and increasing the permeability of the tumor site by 150 %. Analysis of SKOV3 TR cells and the SKOV3 TR xenograft model in BALB/c-nude mice showed a significant decrease in P-glycoprotein levels

in heterogeneous tumor sites, release of paclitaxel, and subsequent induction of apoptosis [48]. A decrease in expression in tumor tissues compared to normal was also noted for let-7g, which may be associated with acquired chemoresistance in late-stage patients. Thus, let-7g acts as a tumor suppressor and can be used to inhibit EOC progression and resistance to cisplatin-based chemotherapy. Similar results were obtained for let-7i. In particular, low levels of let-7i expression in tissues and in vitro cause low sensitivity to cisplatin [54].

Research on the miR-200 family in relation to drug resistance in OC is inconsistent. In vitro experiments have shown that miR-200c expression falls 4- to 5-fold compared to normal levels in tissues with observed paclitaxel resistance. At the same time, miR-200c reduces the sensitivity of cells to carboplatin by increasing sensitivity to taxanes [22]. A number of studies have demonstrated that activation of miR-200c, miR-200a and miR-141 increases the sensitivity of OC cell lines to carboplatin and paclitaxel [40, 43]. The work carried out by Liu et al. revealed that increased expression levels of miR-200b and miR-200c contributed to the death of epithelial OC cells in the presence of cisplatin. In addition, it was found that these microRNAs can increase the sensitivity of tumor cells to cisplatin by suppressing DNA methyltransferases (DNMTs) [33].

Table shows the results of studies by different groups of researchers on the expression of microRNAs on cell lines and in ovarian tumor samples, which showed an association with the formation of chemoresistance.

3.Methylation of microRNA genes in ovarian cancer and development of treatment resistance. An important mechanism for inactivation of microRNA genes in malignant neoplasms is methylation of promoter CpG islands. It was revealed that among microRNA genes, hypermethylation of regulatory CpG islands occurs several times more often than among genes encoding proteins, which makes them promising biomarkers. Aberrant methylation of the promoter regions of both suppressor and oncogenic miR-

MicroRNAs involved in the formation of chemoresistance in ovarian cancer

MicroRNA	Chemotherapy	Function	Target/Signal Path	Reference
miR-130a	Cisplatin	Inhibition of proliferation	MDR1/P-gp, PI3K/Akt/PTEN/mTOR XIAP	[30, 53, 56]
miR-374	Cisplatin	Inhibition of proliferation	Akt, VEGF, PTEN, Wnt	[30]
miR -130b	Cisplatin, Paclitaxel	Inhibition of proliferation, increased sensitivity to chemotherapy	MDR1/P-gp, GST-π	[60]
miR-199a	Cisplatin, Paclitaxel, Adriamycin	Inhibition of proliferation, increased sensitivity to chemotherapy	ABCG2	[16]
miR-490-3P	Cisplatin, Paclitaxel	Inhibition of proliferation	ABCC2	[12,42]
miR-133b	Cisplatin, Paclitaxel	Inhibition of proliferation	GST-π, MDR1	[13]
miR-873	Cisplatin, Paclitaxel	Inhibition of proliferation	MDR1	[51]
miR-186	Cisplatin, Paclitaxel	Inhibition of proliferation	MDR1, GST-π, ABCB1	[41]
miR-137	Cisplatin	G1/S cell cycle arrest, proliferation inhibition, chromatin remodeling, sensitization of ovarian cancer cells to cisplatin-induced apoptosis	XIAP, MCL1	[14,31]
miR-142-5p	Cisplatin	Inhibition of drug resistance	*XIAP, BIRC3, BCL2, BCL2L2, MCL1*	[31]
miR-125b	Cisplatin, Paclitaxel	Cell cycle arrest in G2/M, suppression of proliferation and metastasis, increased resistance to therapy	*BCL2, VEGF, VEGFR, IGFR1*	[15,26,39]
семейство miR-let-7	Cisplatin, Paclitaxel	Inhibition of proliferation and stimulation of apoptosis, increasing sensitivity to chemotherapy	Сигнальный путь PI3K/Akt/mTOR, TGFR-2,Ras, циклин D, цитохром С, *EZH2*	[8, 27, 34, 37,52, 54]
семейство miR-200	Cisplatin, Paclitaxel, Carboplatin	Overexpression of microRNAs of the miR-200 family suppresses the tumorigenicity of OC stem cells by inhibiting EMT; suppresses proliferation and induces apoptosis in tumor cells; reduces migration and invasive activity; suppresses resistance to chemotherapy	*ZEB1, ZEB2, VIM, CREB1*	[10, 33, 44]
miR-34a	Cisplatin	Suppression of proliferation, motility, EMT, invasion, metastasis	*HDAC1, MET, AXL, IL6R, YY1*	[47]
miR-34a-5p	Cisplatin	Inhibition of proliferation and G1-phase cell cycle	PD-L1	[60]

NA genes is involved in all the main processes associated with carcinogenesis: uncontrolled proliferation, bypass of the apoptosis program, neoangiogenesis, the ability to invade and metastasize, etc. [5]. Thus, suppression of apoptosis in tumors is associated with hypermethylation and inactivation of a number of miRNA genes, for example, miR-34b/c, miR-137 and miR-129-2. Methylation of the miR-34b/c and miR-34a loci was observed in tumors of various locations, including ovarian cancer [47,60].

The genes of the miR-200 family have also been shown to be inactivated in tumor cells, associated with hypermethylation. Methylation and decreased expression of these genes is a marker of poor prognosis in ovarian cancer [46].

In a study by Vera et al, the following conclusions were made when examining the effect of miR-7 methylation on platinum resistance. Patients with platinum-sensitive tumors containing unmethylated miR-7 had better progression-free survival rates than patients with methylated miR-7. In addition, patients carrying the unmethylated marker had less aggressive tumors, and overall survival after platinum treatment was three times higher than that of patients with methylated DNA. In addition, the percentage of methylation increased in grade III/IV tumors and in the analysis of highly serous ovarian cancer and platinum-resistant tumors. Thus, miR-7 methylation may play a role as a clinical tool predicting aggressive behavior of this malignancy and poorer response to platinum-based treatment [44].

Recent work by Pernar Kovač et al., through microRNA and cDNA profiling and subsequent integrative analysis, identified the epigenetically regulated and prognostic miR-103a, which plays a role in the migration and invasion of carboplatin-resistant ovarian cancer cells that have acquired a mesenchymal-like phenotype [27].

Russian scientists found that miR-9-1, miR-9-3, miR-107, miR-1258, and miR-130b were methylated in the majority of tumor samples compared to paired normal tissue samples. Moreover, methylation of miR-9-1, miR-9-3 and miR-130b correlated with disease progression [9]. Another work by this team assessed the clinical significance of methylation of 13 microRNA genes (miR -124a-2, miR -124a-3, miR -125-B1, miR -127, miR -129-2, miR -132, miR-137, miR -203a, miR -34b/c, miR -375, miR-9-1, miR-9-3, miR-339) in 26 patients with ovarian cancer. For all 13 genes, an increase in the level of methylation was detected during the transition from unchanged tissue to primary tumors and further from primary tumors to peritoneal metastases, and in the genes miR-203a, miR-375 and miR-339 the level of methylation in metastases increased most significantly (2 or more times). Analysis of microRNA gene methylation in clinical samples of ovarian cancer showed the connection of the observed molecular changes with both the initial stages of tumorigenesis and the progression and dissemination of ovarian cancer, with the presence of metastases in the greater omentum and with the appearance of ascites [36].

Conclusion. Ovarian cancer remains one of the most common causes of death from gynecological cancer in women worldwide. Due to its insidious onset, most patients in the early stages of the disease do not have specific manifestations or symptoms. The lack of a sensitive and effective clinical screening technique results in most cases being diagnosed at late stages. Standard treatment includes platinum-based chemotherapy, and most tumors develop resistance to therapeutic drugs [52].

MicroRNAs (miRNAs) are a group of small non-coding RNA molecules of 19–25 nucleotides that have demonstrated important regulatory functions in cancer over the past decade. Because they are involved in various biological processes as well as post-transcriptional gene regulation, it has been shown that their dysregulation through genetic or epigenetic modifications may contribute to the development of cancer and they may be involved in the development of chemoresistance. Available evidence suggests that they can be considered either oncogenes or tumor suppressor genes, depending on their specific role and level of expression [4].

Numerous miRNAs have been investigated for their potential involvement in ovarian cancer chemoresistance, including miRNA -21, miRNA -29, miRNA -30-5p, miRNA -34a, miRNA -98-5p, miRNA -125b, miRNA -130a, miRNA - 130b, miRNA -133b, miRNA-136, miRNA 137, miRNA -142-5p, miR-146a-5p, miRNA -186, miRNA -199a, miRNA -374a, miRNA -383-5p, miRNA -490-3p, miRNA -503-5p, miRNA -708, miRNA -873, miRNA -1246, miRNA -200 and miRNA-7 families and many others.

A new approach to determining the role of microRNA is to analyze its epigenetic regulation, for example, the methylation status of promoter CpG islands. MicroRNA gene hypermethylation profiles have been proposed as potential markers for the diagnosis and prognosis of cancer of various localizations [47]. At the same time, the analysis of hypermethylation of microRNA genes in ovarian cancer is limited to single studies and requires further research [9, 36].

However, it can be concluded that the current findings on the role of microRNAs in the pathogenesis of ovarian cancer may be useful in assessing the prognosis of metastasis and drug resistance of the tumor, as well as for the selection of new targets for targeted therapy.

The work was carried out with financial support from a grant from the Russian Science Foundation (agreement No. 23-24-00452 dated January 13, 2023).

References

1. Aushev V.N. MikroRNK: malye molekuly s bol'shim znacheniem [MicroRNA: small molecules with great significance]. Klinicheskaya onkogematologiya. Fundamental'nye issledovaniya i klinicheskaya praktika [Clinical oncohematology. Basic research and clinical practice. 2015; 8(1): 1-12 (In Russ.).]

2. Braga E.A., Fridman M.V., Kushlinsky N.E. Molekulyarnye mekhanizmy v metastazirovanii raka yaichnikov: klyuchevye geny i regulyatornye mikroRNK [Molecular mechanisms in ovarian cancer metastasis: key genes and regulatory microRNAs]. Biohimiya [Biochemistry. 2017; 82 (5): 717-731 (In Russ.).]

3. Gershtein E.S. [et al.]. Klinicheskie perspektivy issledovaniya mikroRNK pri rake yaichnikov [Clinical prospects for the study of microRNAs in ovarian cancer]. Onkoginekologiya [Oncogynecology. 2016; 3:4-16 (In Russ.).]

4. Kushlinsky N.E. [et al.]. Klinicheskaya znachimost' metilirovaniya gruppy genov mikro-rnk u bol'nyh rakom yaichnikov [Clinical significance of methylation of a group of microRNA genes in patients with ovarian cancer]. Klinicheskaya laboratornaya diagnostika [Clinical laboratory diagnostics. 2020; 65 (5): 321-327 (In Russ.).] DOI: http://dx.doi.org/10.18821/0869-2084-2020-65-5-321-327

5. Loginov V.I. [et al.] Metilirovanie genov mikroRNK i onkogenez (obzor) [Methylation of microRNA genes and oncogenesis (review)]. Biohimiya [Biochemistry. 2015; 80(2): 184-203 (In Russ.).]

6. Agostini A. [et al.] The microRNA miR-192/215 family is upregulated in mucinous ovarian carcinomas. Scientific reports. 2018; 8(1): 11069.

7. Bendoraite A. [et al.] Regulation of miR-200 family microRNAs and ZEB transcription factors in ovarian cancer: evidence supporting a mesothelial-to-epithelial transition. Gynecologic oncology. 2010; 116(1): 117-125. doi: 10.1016/j.ygyno.2009.08.009

8. Biamonte F. [et al.] MicroRNA let-7g acts as a tumor suppressor and predictive biomarker for chemoresistance in human epithelial ovarian cancer. Scientific reports. 2019; 9 (1): 5668. DOI https://doi.org/10.1038/s41598-019-42221-x

9. Braga E.A. [et al.] Five hypermethylated microRNA genes as potential markers of ovarian cancer. Bulletin of Experimental Biology and Medicine. 2018; 164: 351-355.

10. Brozovic A. [et al.] The miR-200 family differentially regulates sensitivity to paclitaxel and carboplatin in human ovarian carcinoma OVCAR-3 and MES-OV cells. Molecular oncol-

ogy. 2015; 9(8): 1678-1693. doi: 10.1016/j.molonc.2015.04.015

11. Calin G.A. [et al.] Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci USA. 2002; 99: 15524-15529.

12. Chen S. [et al.]. MicroRNA 490-3P enhances the drug-resistance of human ovarian cancer cells. Journal of ovarian research. 2014; 7(1): 1-6.

13. Chen S. [et al.] MicroRNA-133b targets glutathione S-transferase π expression to increase ovarian cancer cell sensitivity to chemotherapy drugs. Drug design, development and therapy. 2015: 5225-5235. doi: 10.2147/DDDT.S87526

14. Chen W. [et al.] MicroRNA-137 downregulates MCL1 in ovarian cancer cells and mediates cisplatin-induced apoptosis. Pharmacogenomics. 2020; 21(3): 195-207. doi: 10.2217/pgs-2019-0122.

15. Chen Z. [et al.] Serum miR-125b levels associated with epithelial ovarian cancer (EOC) development and treatment responses. Bioengineered. 2020; 11(1): 311-317. doi: 10.1080/21655979.2020.1736755

16. Cheng W. [et al.] MicroRNA-199a targets CD44 to suppress the tumorigenicity and multidrug resistance of ovarian cancer-initiating cells. The FEBS journal. 2012; 279 (11): 2047-2059.

17. Choi P.W. [et al.] Characterization of miR-200 family members as blood biomarkers for human and laying hen ovarian cancer. Scientific reports. 2020; 10(1): 20071. doi: 10.1038/s41598-020-77068-0

18. Forterre A. [et al.] A comprehensive review of cancer MicroRNA therapeutic delivery strategies. Cancers. 2020; 12 (7): 1852. doi: 10.3390/cancers12071852

19. Ghafouri-Fard S., Shoorei H., Taheri M. miRNA profile in ovarian cancer // Experimental and molecular pathology. 2020; 113: 104381. DOI: 10.1016/j.yexmp.2020.104381

20. Global Cancer Observatory [Electronic resource] URL: https://gco.iarc.fr/ (access date: 10/08/2023)

21. Hu Y. [et al.] Oncogene miR-934 promotes ovarian cancer cell proliferation and inhibits cell apoptosis through targeting BRMS1L. European Review for Medical & Pharmacological Sciences. 2019; 23 (13).

22. Ibrahim F.F. [et al.] MicroRNA-200c and microRNA-31 regulate proliferation, colony formation, migration and invasion in serous ovarian cancer. Journal of ovarian research. 2015; 8(1): 1-14. doi: 10.1186/s13048-015-0186-7

23. Iorio M. V., Croce C. M. MicroRNAs in cancer: small molecules with a huge impact // Journal of clinical oncology. 2009; 27(34): 5848. doi: 10.1200/JCO.2009.24.0317

24. Jia Y. [et al.] MicroRNA-34 suppresses proliferation of human ovarian cancer cells by triggering autophagy and apoptosis and inhibits cell invasion by targeting Notch 1. Biochimie. 2019; 160:193-199.

25. Kazmierczak D. [et al.] The significance of MicroRNAs expression in regulation of extracellular matrix and other drug resistant genes in drug resistant ovarian cancer cell lines. International Journal of Molecular Sciences. 2020; 21(7): 2619.

26. Kong F. [et al.] MiR-125b confers resistance of ovarian cancer cells to cisplatin by targeting pro-apoptotic Bcl-2 antagonist killer 1. Journal of Huazhong University of Science and Technology [Medical Sciences]. 2011; 31:543-549.

27. Kovač M. P. [et al.] MiRNA-mRNA integrative analysis reveals epigenetically regulated and prognostic miR-103a with a role in migration and invasion of carboplatin-resistant ovarian cancer cells that acquired mesenchymal-like phenotype//Biomedicine & Pharmacotherapy. 2023; 166: 115349. doi: 10.1016/j.biopha.2023.115349

28. Lee R. C., Feinbaum R. L., Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993; 75(5): 843-854.

29. Li J., Shao W., Feng H. MiR-542-3p, a microRNA targeting CDK14, suppresses cell proliferation, invasiveness, and tumorigenesis of epithelial ovarian cancer. Biomedicine & Pharmacotherapy. 2019;110: 850-856.

30. Li N. [et al.] MiR-130a and MiR-374a function as novel regulators of cisplatin resistance in human ovarian cancer A2780 cells. PloS one. 2015; 10(6): e0128886.

31. Li X. et al. MicroRNA-137 promotes apoptosis in ovarian cancer cells via the regulation of XIAP. British journal of cancer. 2017; 116 (1): 66-76. doi: 10.1038/bjc.2016.379

32. Li X. et al. MiR-142-5p enhances cisplatin-induced apoptosis in ovarian cancer cells by targeting multiple anti-apoptotic genes. Biochemical pharmacology. 2019; 161:98-112.

33. Liu J. [et al.] MiR-200b and miR-200c co-contribute to the cisplatin sensitivity of ovarian cancer cells by targeting DNA methyltransferases. Oncology Letters. 2019; 17 (2): 1453-1460. doi: 10.3892/ol.2018.9745.

34. Liu J., Chen W., Zhang H., Liu T., Zhao L. MiR-214 targets the PTEN-mediated PI3K/Akt signaling pathway and regulates cell proliferation and apoptosis in ovarian cancer. Oncology letters. 2017; 14: 5711–5718. doi: 10.3892/ol.2017.6953

35. Liu Y. [et al.] MiR-214 suppressed ovarian cancer and negatively regulated semaphorin 4D. Tumor Biology. 2016; 37: 8239-8248. doi: 10.1007/s13277-015-4708-0

36. Loginov V.I. [et al.] Aberrant methylation of 20 miRNA genes specifically involved in various steps of ovarian carcinoma spread: from primary tumors to peritoneal macroscopic metastases. International Journal of Molecular Sciences. 2022; 23 (3): 1300. DOI: 10.3390/ijms23031300

37. Lu L. [et al.] MicroRNA let-7a: a potential marker for selection of paclitaxel in ovarian cancer management. Gynecologic oncology. 2011; 122 (2): 366-371. doi: 10.1016/j.ygyno.2011.04.033

38. O'Brien J., Hayder H., Zayed Y., Peng C. Overview of microRNA biogenesis, mechanisms of actions, and circulation. Frontiers in Endocrinology. 2018; 9: 402. DOI: 10.3389/fendo.2018.00402

39. Parayath N. N. [et al.] Improved anti-tumor efficacy of paclitaxel in combination with MicroRNA-125b-based tumor-associated macrophage repolarization in epithelial ovarian cancer. Cancer letters. 2019; 461: 1-9. doi: 10.1016/j.canlet.2019.07.002

40. Prislei S. [et al.] MiR-200c and HuR in ovarian cancer. BMC cancer. 2013; 13: 1-14.

41. Sun K. X. [et al.] MicroRNA-186 induces sensitivity of ovarian cancer cells to paclitaxel and cisplatin by targeting ABCB1. Journal of ovarian research. 2015;8: 1-7.

42. Tian J. [et al.] MiR-490-3p sensitizes ovarian cancer cells to cisplatin by directly targeting ABCC2. American journal of translational research. 2017; 9 (3): 1127.

43. Van Jaarsveld M. T. M. [et al.] MiR-141 regulates KEAP1 and modulates cisplatin sensitivity in ovarian cancer cells. Oncogene. 2013; 32 (36): 4284-4293. doi: 10.1038/onc.2012.433

44. Vera O. [et al.] DNA methylation of miR-7 is a mechanism involved in platinum response through MAFG overexpression in cancer cells. Theranostics. 2017; 7 (17): 4118. doi: 10.7150/thno.20112.

45. Vilming Elgaaen B. [et al.] Global miRNA expression analysis of serous and clear cell ovarian carcinomas identifies differentially expressed miRNAs including miR-200c-3p as a prognostic marker. BMC cancer. 2014; 14 (1): 1-13.

46. Vinogradov S., Wei X. Cancer stem cells and drug resistance: the potential of nanomedicine. Nanomedicine. 2012; 7 (4): 597-615.

47. Vogt M. [et al.] Frequent concomitant inactivation of miR-34a and miR-34b/c by CpG methylation in colorectal, pancreatic, mammary, ovarian, urothelial, and renal cell carcinomas and soft tissue sarcomas. Virchows Archiv. 2011; 458:313-322.

48. Wang X. [et al.] A novel targeted co-delivery nanosystem for enhanced ovarian cancer treatment via multidrug resistance reversion and mTOR-mediated signaling pathway. Journal of Nanobiotechnology. 2021; 19 (1): 1-18. doi: 10.1186/s12951-021-01139-1

49. Wang Z. [et al.] Integrated microarray meta-analysis identifies miRNA-27a as an oncogene in ovarian cancer by inhibiting FOXO1. Life sciences. 2018; 210: 263-270. https://doi.org/10.1016/j.lfs.2018.08.043

50. Wanjia T. [et al.] Extracellular vesicles in ovarian cancer chemoresistance, metastasis, and immune evasion. Cell Death and Disease. 2022; 13 (1). DOI: 10.1038/s41419-022-04510-8

51. Wu D. [et al.] MicroRNA-873 mediates multidrug resistance in ovarian cancer cells by targeting ABCB1. Tumor Biology. 2016; 37: 10499-10506.

52. Xie W. [et al.] Ovarian cancer: epigenetics, drug resistance, and progression. Cancer cell international. 2021; 21: 1-16. doi: 10.1186/s12935-021-02136-y

53. Yang L. [et al.] Altered microRNA expression in cisplatin-resistant ovarian cancer cells and upregulation of miR-130a associated with MDR1/P-glycoprotein-mediated drug resistance. Oncology reports. 2012; 28 (2): 592-600. doi: 10.3892/or.2012.1823

54. Yang N. [et al.] MicroRNA microarray identifies Let-7i as a novel biomarker and therapeutic target in human epithelial ovarian cancer. Cancer research. 2008; 68 (24): 10307-10314. doi: 10.1158/0008-5472.CAN-08-1954

55. Zhang B. [et al.] High expression of microRNA-200a/b indicates potential diagnostic and prognostic biomarkers in epithelial ovarian cancer. Disease Markers. 2022. doi: 10.1155/2022/2751696

56. Zhang X. [et al.] Downregulation of miR-130a contributes to cisplatin resistance in ovarian cancer cells by targeting X-linked inhibitor of apoptosis (XIAP) directly. Acta Biochim Biophys Sin. 2013; 45 (12): 995-1001.

57. Zhao C., Sun X., Li L. Biogenesis and function of extracellular miRNAs. ExRNA. 2019; 1(1): 1-9.

58. Zhao Y., Butler E. B., Tan M. Targeting cellular metabolism to improve cancer therapeutics. Cell death & disease. 2013; 4 (3): e532-e532. doi: 10.1038/cddis.2013.60

59. Zong C., Wang J., Shi T. M. MicroRNA 130b enhances drug resistance in human ovarian cancer cells. Tumor Biology. 2014; 35: 12151-12156.

60. Zuo Y. [et al.] MiR-34a-5p PD-L1 axis regulates cisplatin chemoresistance of ovarian cancer cells. Neoplasma. 2020; 67 (1): 93-101.