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Micro-RNA Mediated Signalling Circuits in Endocrine-Dependent Malignancies of Human Reproductive System

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Abstract
Breast, ovarian, endometrial, prostate and cervical cancers are considered as the major endocrine-dependent malignancies associated with human reproductive system. Current tools used for diagnosis and therapeutics of these malignancies mainly exploit the hormone-sensitivity associated with them. Nonetheless, they often fail to give appreciable outcomes in terms of prognosis and survival rates. miRNAs have emerged as one of the key players dictating the pathophysiology of endocrine-dependent malignancies and present themselves as apt candidates to be developed as potential biomarkers or therapeutic targets for the early prognosis as well as treatment of these diseases. In this review, we have high-lighted the regulatory networks controlled by the promising candidate miRNAs in the pathophysiology of the major endocrine-dependent reproductive system-associated malignancies.

Keywords: Breast Cancer, Cervical Cancer, Endometrial Cancer, miRNA, Ovarian Cancer, Prostate Cancer

1. Introduction
miRNAs are ~22 nucleotides long, small non-coding RNA molecules that regulate the expression of specific target genes at post-transcriptional levels. miRNAs play key regulatory roles in a variety of biological processes like cell proliferation, differentiation, apoptosis, etc.[1]. The genes that encode miRNAs harbor ~3% of human genome, which in turn may regulate one-third of human protein coding genes[2]. The miRNAs have been implicated in the regulation of reproductive physiology, where they engage in regulation at different stages, such as at sex differentiation, gametogenesis, fertilization, implantation etc.[3-6]. Therefore, any discrepancy associated with the expression pattern of miRNAs can cause adverse impact on the proteome, which in turn can lead to a variety of pathological effects. miRNAs have also been reported to be involved in the pathophysiology of human reproductive system. The malignancies associated with reproductive system are mostly fuelled by hormones and such malignancies include ovarian cancer, endometrial cancer, prostate cancer, breast cancer, etc.[7-10]. The present review is focused on highlighting the involvement of miRNAs in the regulation of candidate, hormone-fuelled malignancies associated with human reproductive system, with a view to provide a holistic platform of information pertaining tosuch miRNAs which would serve as potential biomarkers or therapeutic targets for the prognosis and treatment of reproductive system-associated malignancies.

2. miRNAs: Biogenesis, Molecular Structure and Function
miRNAs include a class of small, single-stranded, non-coding RNAs encompassing ~22 nucleotides in their mature form. miRNAs are encoded by endogenous genes which may get transcribed as independent units either from intronic sequences of protein coding or non- coding

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regions or from intergenic sequences. Some miRNA genes are transcribed as polycistronic primary transcripts, and the genes that code for such miRNAs are located in clusters[11,12].

The miRNA genes are transcribed by RNA polymerase II/III. The primary transcript thus formed is then processed in the nucleus by a microprocessor complex to yield a hair pin like, 60-90 bp long precursor miRNA (pre-miRNA)[13]. The microprocessor is composed of a nuclear ribonuclease III, Drosha and its partner DGCR8, which is a double-stranded RNA binding protein[14,15]. Pre- miRNA is actively transported out of the nucleus by Exportin-5 machinery[16] and within the cytoplasm it is cleaved by an RNase III enzyme namely Dicer assisted with TAR (HIV) RNA Binding Protein (TRBP)[17], yielding ~22 nucleotide long miRNA:miRNA duplex characterised by an overhanging of 2 nucleotides at the 3'end[18]. A strand with relatively unstable base pairing at the 5' end is then incorporated into RNA-Induced Silencing Complex (RISC) in a mechanism dependent on Dicer, TRBP, dsRNA binding proteins of the AGO family, nucleases, helicases, etc.[19,20]. The mature miRNA possesses a 2-8 nucleotide long seed sequence at the 5' end[21]. The miRNA-mediated regulation on target gene expression is orchestrated mainly through the limited base pairing interactions between seed region of miRNA and the complimentary sequence available at the 3'UTR of target mRNA. The imperfect base pairing can result in the destabilization of target mRNA by means of deadenylation, decapping, etc.[22]. miRNA-target interaction may also lead to mRNA sequestration, degradation or storing in processing bodies (p-bodies)[23]. According to a few reports, miRNAs might also interact with the 5' UTR, coding and promoter region of the target gene[1]. A single miRNA can target multiple mRNAs through limited base pairing interactions, indicating the enormous regulatory potential of individual miRNAs.

3. Influence of miRNAs on Endocrine-Dependent Malignancies of Human Reproductive System

3.1 Endocrine-Dependent Malignancies

The endocrine-dependent malignancies constitute one of the most common types of cancers world-wide[7]. Among such carcinomas, breast cancer and cervical constitute the first and fourth most common cancers, respectively, among women[8]. Ovarian hormones such as estrogen and progesterone have been reported to play key role in the development of breast cancer. In addition, pituitary hormones such as prolactin and growth hormone have also been implicated in breast cancer development[24]. Estradiol (E_2) and progesterone (P_4) have been implicated in promoting carcinogenesis of cervical tissue[25]. Prostate cancer is the second most common cancer among men globally[9]. The male sex hormone, androgens, has been implicated to play key role in the progression of prostate cancer[26]. Further, ovarian cancer and endometrial cancer have also been reported to be fuelled by hormones. The ratio of estrogen to progesterone has been shown to play a crucial role in endometrial carcinogenesis[10]. Gonadotrop in releasing hormone and its synthetic analogues have been reported to exert anti-proliferative effect on ovarian cancer cell lines[27]. In addition, the constitutive expression of progesterone receptors has been implicated in the development of ovarian neoplasm[28]. The regulatory role of candidate miRNAs in the pathogenesis of major hormone-dependent malignancies of human reproductive system is discussed hereunder.

3.2 miRNAs in Breast Cancer

Breast Cancer (BC) is said to be the most prevalent malignancy and the leading cause of cancer-related deaths among women world-wide[8]. Approximately, 70% of all malignancies associated with breast tissue belong to the hormone receptor-positive category. Endocrine therapy, practiced in such types of breast cancers, though effective in half of the population, developed complications associated with endocrine resistance in the remaining other half[29]. miRNAs have been implicated to play key role in the pathophysiology of BC and many of these have been identified to be potent therapeutic targets. The recent reports in this regard are discussed.

Ye and his team have reported that the migration and invasion of breast cancer cells were monitored by miR-429 via regulating the expression of its target genes, including ZEB1 and CRK[30]. Further, an oncogenic miRNA, miR-9, has been implicated to play key role in the regulation of BC cell metastasis. miR-9-mediated effect on metastasis was found to be orchestrated via its target genes, E-cadherin and FOXO1[32-35]. Similarly, miR-223 has been reported to promote BC cell proliferation by targeting FOXO1[31].

miR-940 has been implicated inFOXO3-dependent induction of cell proliferation and invasion in BC[46]. According to a report by Zhao and his group, miR-145 is involved in the regulation of cell migration and EMT by targeting FSCN-1 gene in BC[37]. However, miR-421 has been reported to inhibit BC cell metastasis by targeting metastasis-associated 1 gene (MTA1)[44]. A report by Fong *et al*., have shed light on the role of a secretory miRNA in modulating the glucose metabolism in the neighbouring cells. The authors suggested that secretory miR-122 in BC plays key role to increase the nutrient availability in the premetastatic niche, by modulating the expression levels of pyruvate kinase in the recipient non-cancerous cells[36] (Figure 1).

Further, the expression of miR-183/-96/-182 cluster was found to be upregulated in BC and it was found to be involved in facilitating cell proliferation and migration. Interestingly, miR-182 of the cluster was found to regulate the expression of RAB21 gene[38]. A report by Wu *et al*., suggests that miR-30b-5p acts to switch on AKT signalling in BC cell line by regulating the expression level of ASPP2 gene, and such a regulation has been reported to cause cell proliferation, migration and invasion[39]. Further, a recent gene knock out study by Hannafon and his group has revealed the oncogenicity of two candidate miRNAs including miR-23b and miR-27b, in MCF7 cell line[40]. Further, miR-142-3p, by targeting HMGB1, has been reported to promote drug sensitivity and apoptosis of BC cells and, hence, the miR-142-3p/HMGB1 axis was suggested to be a potent therapeutic target to manage drug resistance of BC patients[41]. In addition, miR-205-3p and miR-18 have been reported to be associated with poor prognosis of BC patients, where miR-18 has been reported to exert its effect by initiating wnt signalling pathway[42,43].

A report by Sharma *et al*., has revealed that miR-191-5p inhibits apoptosis in BC cell lines by directly targeting SOX4 gene and, further, p53 has been identified to be a negative regulator of miR-191-5p expression[45]. Similarly, miR-21 has been reported to promote cell

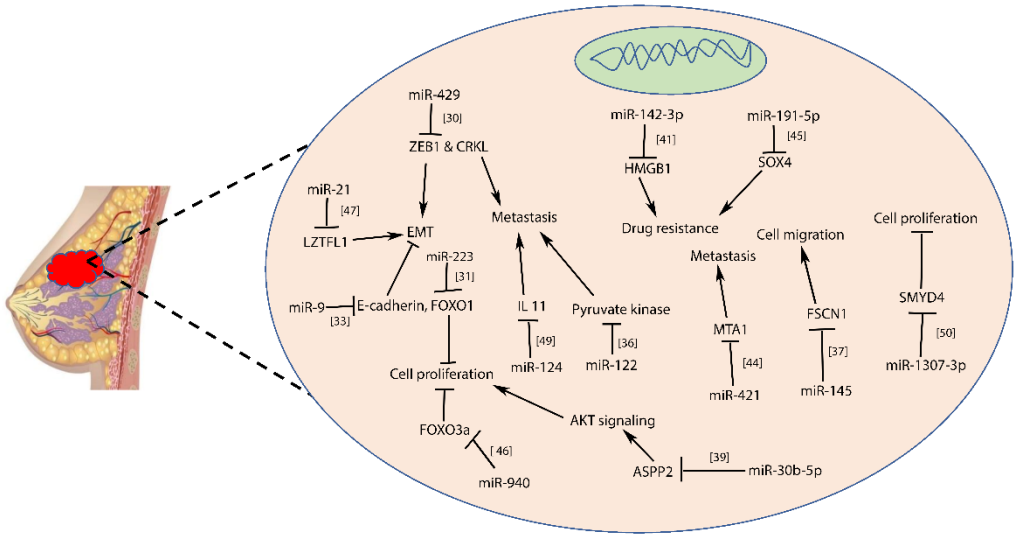

Figure 1. Micro-RNAs in breast cancer: miR-429, miR-21 and miR-9 are involved in the regulation of epithelial to mesenchymal transition in breast cancer cells by targeting Zinc finger E-box binding homeobox 1, Leucine zipper transcription factor like 1 and E-cadherin, respectively. miR-223 and miR-9 are involved in the regulation of cell proliferation by targeting Forkhead box protein O1, while, miR-940 regulates cell proliferation by targeting Forkhead box protein O3a. miR-30b-5p-mediated inhibition of 'Apoptosis-stimulating of p53 protein 2' was found to be associated with the activation of AKT signaling, leading to cell proliferation. miR-1307-3p has been implicated to regulate cell proliferation by targeting SET and MYND domain containing 4. miR-122, miR-124, miR-421 and miR-429 regulated breast cancer cell metastasis by targeting Pyruvate kinase, Interleukin 11, Metastasis associated 1 and CRK Like Proto-Oncogene, Adaptor protein respectively. miR-145 regulates cell migration by targeting Fascin Actin-Bundling Protein 1, whereas, miR-142-3p and miR-191-5p modulate acquisition of drug resistance by targeting high mobility group box 1 and SRY-box transcription factor 4, respectively.

proliferation and metastasis in BC cells and it appears to target LZTFL1 gene, whose protein counterpart has been reported to regulate β-catenin signalling, promoting the process of EMT[47]. In addition, Yan *et al.,* have reported that knockdown of miR-21 in BC cell line prevents cell proliferation, migration and tumorigenesis[48]. Further, miR-124 has been reported to prevent metastasis of BC cells by targeting interleukin -11[49]. In addition, Han *et al*., have reported that miR-1307-3p targets SMYD4, a tumor suppressor gene, and thereby promote BC cell proliferation and tumorigenesis[50].

3.3 miRNAs in Ovarian Cancer

Ovarian Cancer (OC) is the 6th most common malignancy in women. OC is characterised by the malignant transformation of ovarian epithelial cells, stromal cells, germ cells or cells of sex cords, wherein epithelial cells are the most frequent committed ones[51]. The OC cells exhibit four different histological sub-types, serous, endometroid, mucinous and clear cells. Serous cell is the most common among them. Each histological sub-type exhibits distinct morphology and genetic alterations[52]. The prognosis of OC is relatively tedious due to the subtle progressive nature of the disease in the early stage and the acquisition of drug resistance by the OC cells, hence it demands novel therapeutic interventions for the early stage prognosis and treatment. Numerous tumor suppressor/oncogenic miRNAs have been reported to be associated with OC tumorigenesis, and such recent reports are reviewed here.

miR-424-5p, which has been reported to be significantly down-regulated in Epithelial Ovarian Cancer (EOC) tissue and cell lines, upon being restored of its function, targets CCNE1 the gene coding for G1/S-specific cyclin-E1 protein, and leads to inhibition of E2F1-pRb pathway and associated cell cycle arrest at G1/G0 phase[53]. Evasion of immune system is one of the important hallmarks of carcinogenesis. Programmed cell death-1 (PD-1) and T-lymphocyte-associated antigen-4 (CTLA-4) were reported to be the major immunomodulatory receptors on T cells, which interact with PD-L1 on macrophages and CD80 on dendritic cells, respectively. It has been reported that in EOC, miR-424(322) targets PD-L1 and CD80, which in turn contribute to acquisition of chemoresistance[54]. Further, miR-424-3p has been reported to sensitize OC cells to cisplatin by targeting galectin-3 gene[55].

miR-145 was found to be down-regulated in OC tissues, cell lines and also in serum samples of OC patients. P70S6K1 was found to be one of the direct targets of miR-145, which, in an AKT/mTOR/P70S6K1 axis-dependent manner, promoted the expression of G1 cyclins and regulated cell cycle progression[56,57]. In addition, MUC1 gene was found to be another target, which induces metastasis by promoting the expression of matrix metalloproteinase 13[58]. MUC1-dependent transcriptional activation of genes was found to be mediated by wnt/β-catenin signalling[59]. miR-145 was found to be down-regulated in response to cisplatin treatment in cisplatin-resistant OC cells, and it contributed to the immune tolerance of cisplatin-resistant OC cells by targeting c-Myc, thereby regulating the expression of programmed cell death ligand 1 (PD-L1)[60]. In addition, cyclin D2 (CCND2) and E2F transcription factor 3 (E2F3), two major regulators of cell cycle progression, were found to be the direct targets of miR-145 in OCs, and the rescued expression of E2F3 and CCND2, upon the down regulation of miR-145 in OCs, promoted cell cycle progression[61]. In a different study, SMAD4, a mediator of TGFβ signalling pathway, was found to be a direct target of miR-145-5p in EOC cells, and the rescued expression of SMAD4, upon down regulation of miR-145-5p, contributed to cell proliferation and migration[62]. High-Grade serous Ovarian Carcinoma (HGOC) is a type of aggressive EOC characterized by loss of function mutation in TP53 gene. miR-145 was found to be down-regulated in HGOC, where metadherin (MTDH), a protein that promotes tumor cell proliferation, was found to be its target, and this study established a link between p53, miR-145 and MTDH[63].

miR-125b is another miRNA which was found to be down-regulated in OC-, and PPARγ-mediated induction of miR-125b expression induced growth suppression by targeting BCL3, a proto-oncogene[64]. Ectopic expression of miR-125b was found to be negatively regulating the process of Epithelial-to-Mesenchymal Transition (EMT) by targeting the S100A4 and SET genes[65,66]. Laminin γ2 (LAMC2) has been reported to promote OC progression by activating p38 MAPK signalling in a miR-125a-5p-dependant mechanism[67]. However, miR-125b has been reported to be upregulated in cisplatin resistant OC cells and its contribution to the acquisition of resistance was reported to be by targeting pro-apoptotic BAK1 gene[68].

miR-100 has also been reported to be down-regulated in OC, where it was found to target Polo-Like Kinase 1

(PLK1), a serine/threonine kinase that regulate mitosis at different stages[69,70]. In addition, it has also been reported that miR-100 re-sensitizes resistant EOCs to cisplatin by negatively regulating the expression of mTOR and PLK1[71]. miR-100 along with miR-22 was found to elicit tumor suppressor activity by targeting multiple components of PI3K/AKT/MTOR signalling pathway[72].

Further, miR-377 has been reported to be down-regulated in OCs and it showed tumor suppressor activity when ectopically expressed, by targeting JAG1 and CUL4A genes[73,74]. miR-124 has also been reported to be down-regulated in OC, where it was reported to target SPHingosine Kinase 1 (SphK1) and Programmed Cell Death 6 (PDCD6) genes, thereby contributing to cell proliferation, migration, invasion and evasion of apoptosis[75,76]. miR-362-3p was found to exhibit anti-proliferative role in EOC by targeting MyD88 mRNA[77]. In addition, miR-490-3p was found to sensitize OCs towards cisplatin by directly targeting ABCC2 gene[78].

Further, let-7d-5p was found to be down-regulated in OC and the ectopic expression of this miRNA promoted sensitivity of cells to cisplatin and also induced apoptosis by regulating HMGA1 gene and the p53 pathway[79]. However, let-7d-3p was found to be upregulated in OC cells which was associated with the positive response of OC patients to chemotherapy involving carboplatin/ placlitaxel. Further, the *in-silico* target prediction analysis indicated that the predicted targets of let-7d-3p were involved in pathways associated acquisition of drug resistance, and such targets include HIF-1, ABC transporters, RAS and ERbB signalling[80].

A study by Kleemann *et al.*, has revealed that transfection of OC cells with miR-493-3p mimic induce apoptosis by targeting multiple genes including AKT2, HMGA2, STK38L, ETS1 and E2F5[81]. In a different study by Tambe *et al.*, Mitotic Arrest Deficiency-2 (MAD2), an important factor of spindle assembly check point, was found to be one of the direct targets of miR-493-3p. Further, the elevated level of miR-493-3p was found to be associated with the reduced survival rate of OC patients with aggressive tumor under paclitaxel therapy[82].

Giannakakis and his group reported that one of the hypoxia-responsive miRNAs, miR-210, was involved in controlling cell cycle progression by negatively regulating E2F3 and further that the gene coding for miR-210 was often deleted in OC[83]. According to a study by Jin *et al.*, the sensitivity of OC cells towards cisplatin was found to be dependent on miR-210-3p mediated regulation on E2F3[84]. Further, a study by Ding *et al.* revealed that in SKOV3 ovarian cell line, miR-210, was involved in the promotion of OC cell migration via promoting EMT[85]. Li and his group have reported that in response to HIF1α, miR-201 was upregulated in OC cell lines, and it was found to inhibit apoptosis by targeting PTPN1 gene[86], a negative regulator of pro-survival- RTK signalling[87].

miR-216b has been reported to promote cisplatin sensitivity in OC cells by targeting PARP1[88]. Similarly, miR-31 has also been reported to contribute to cisplatin resistance in OC cells by negatively regulating KCNMA1 expression, which is a subunit of calcium-regulated big potassium channel[89]. Further, it has been reported that down-regulation of miR-31 imparts taxane resistance in OC cells by promoting the expression of receptor tyrosine kinase MET[90]. According to Hassan *et al.,* miR-31 targets Stathmin 1 (STMN1) gene, a depolymerizer of microtubule, thereby contributes to taxane resistance in OC[91,92].

Wu *et al.* have reported that miR-22 was down-regulated in OC cells and further that it promoted EMT and cell viability by modulating the levels of NLRP3 mRNA and, regulating PI3K/AKT pathway[93]. According to a study by Li, *et al.*, the ectopic expression of miR-22 in OC cell lines promoted apoptosis, suppressed cell viability and autophagy by negatively regulating Notch signalling pathway[94]. Similarly, the expression of miR-106b was found to be significantly low in EOC when compared to normal ovarian tissue and benign tumors. Further, the ectopic expression of miR-106b was found to inhibit tumor progression by targeting RhoC, suggesting miR-106b to be a promising therapeutic candidate to be used for the treatment of EOC[95].

miR-99a was found to act as a tumor suppressor miRNA in OC, and its expression was found to be significantly low in both OC tissue specimen and cell lines. The gain of function studies of miR-99a revealed that it suppressed OC cell proliferation and invasion by modulating AKT/mTOR signalling pathway and also by regulating the process of EMT, in a HOXA1 target gene-dependent mechanism[96].

miR-9 and miR-223 were identified as two major biomarkers of recurrent OC[97]. Further, miR-9 has been reported to target E-cadherin in serous OC cells, which thereby promoted metastasis. The inhibitory effect of miR-9 on E-cadherin, has also been reported to promote EMT in OC[98]. It has also been reported to target BRCA1 gene in OC and it further prevented DNA damage

repair and sensitized OC cells to chemotherapy[99]. In addition, miR-9 has also been reported to target Talin1 (TLN1) gene in OC[100]. According to a study by Zhang *et al*., circPLEKHM3, one of the most significantly down-regulated circular RNA (circ RNA) in OC tissues, was found to exhibit tumor suppressor effect by targeting miR-9/BRCA1/DNAJB6/KLF4/AKT1 axis[101].

miR-137 has been reported to promote cisplatin induced apoptosis in OC cells by targeting XIAP[102], an anti-apoptotic protein that inhibits the activities of caspases-3, -7, and -9[103]. Further, Sun *et al.*, reported that in cisplatin-resistant OC cells, the increased ROS level caused c-Myc mediated transcriptional repression of miR-137, which led to the rescue of its target gene EZH2 which in turnaccelerated cellular survival pathways. Further, c-Myc mediated recruitment of EZH2 to miR-137 promoter has also been reported to be involved in enhancing the repression of miR-137 gene[104]. Dong *et al*. reported that OC tissue possesses significantly low levels of both miR-137 and miR-34a, and these miRNAs directly target Snail gene thereby negatively regulating the process of EMT, invasiveness and sphere forming ability of OC cells[105]. In OC cells, miR-137 has also been reported to target AEG-1/ Metadherin gene[106]. AEG-1, when over-expressed, has been implicated to promote tumor cell proliferation, invasion, metastasis and chemoresistance[107-109]. MCL1, one of the major anti apoptotic Bcl2, has been reported to be the target of miR-137 in OC[110] (Figure 2).

3.4 miRNAs in Endometrial Cancer

Endometrial Cancer (EC) is said to be the most common gynaecological malignancy globally[111]. It has been classified into two different categories based upon its responsiveness to estrogen. The type 1 EC, also known as the estrogen-dependent endometrioid adenocarcinoma is the most common type, characterised by good prognosis,while the type 2 is non-estrogen-dependent cancer and it has been reported to be highly aggressive[112].

miR-494-3p was found to be significantly up-regulated in endometrial cancer (EC) and it promotes cell proliferation, migration and evasion by targeting PTEN and consequently activating PI3K/AKT signalling pathway[113]. Similarly, miR-191 was found to be up-regulated in EC tissues and it was found to target Ten-Eleven Translocation 1 (TET1). TET1 is a methyl cytosine dioxygenase, the decreased expression of which results in hyper-methylation of promoter sequence of APC, a tumor suppressor gene, with a consequent down-regulation in the expression of APC[114]. The expression of miR-505 was found to be significantly down-regulated in EC tissues and its ectopic expression in EC cells resulted in reduced cell proliferation, migration and invasion with simultaneous increase in the rate of apoptosis. Further, miR-505 was found to target TGFα mRNA and the ectopic expression of miR-505 lead to reduced expression of TGFα with a subsequent reduction in the levels of TGFα responsive proteins like MMP2, MMP9 and CDK2 and increase in the levels of Bax and cleaved PARP, suggesting miR-505 to be a tumor suppressor in EC[115]. Similarly, miR-137 was found to act as a tumor suppressor in EC whose expression was found to be supressed by DNA hypermethylation[116]. In addition, the expression of FOXO1, a tumor suppressor gene, has been reported to be down-regulated in EC. A report by Myatt *et al.*, has suggested that several miRNAs like, miR-9, miR-27, miR-96, miR-153, miR-183 and miR-186 might be responsible for the reduced expression of FOXO1 in EC cell lines[117]. The expression of miR-873 was also found to be significantly down-regulated in EC tissues and cell lines. A study by Wang and Zhu revealed that miR-873, when ectopically expressed in EC cells, targets hepatoma-derived growth factor (HDGF) and thereby inhibits cell proliferation and invasion[118]. Karaayvaz, *et al.*, have suggested miR-205, which was found at significantly high levels in EC tissues, to be a unique biomarker in EC[119]. miR-218, miR-23a and miR-34a have been reported to inhibit EC progression by targeting ADD2[120], SIX1[121] and Notch1[122], respectively. In addition, the over-expression of miR-34b was found to inhibit EC cell growth, migration and invasion. Further, miR-34b has been reported to induce cell cycle arrest, in addition to its capability to induce sensitivity of cells to paclitaxel[123].

According to a report by Wang *et al.*, increased expression of miR-135a in EC contributes to improved cell proliferation, migration and invasion. In addition, they have suggested that in EC, miR-135a regulates the process of EMT by modulating the levels of EMT markers such as E-cadherin, Vimentin, N-cadherin and Snail. According to them, miR-135a also plays key role in modulating the levels of PTEN and p-AKT in EC cells. Further, miR-135a has also been reported to contribute to the acquisition of cisplatin resistance in EC cells, by negatively regulating apoptosis via modulating the expression of BAX and Bcl2 genes[124].

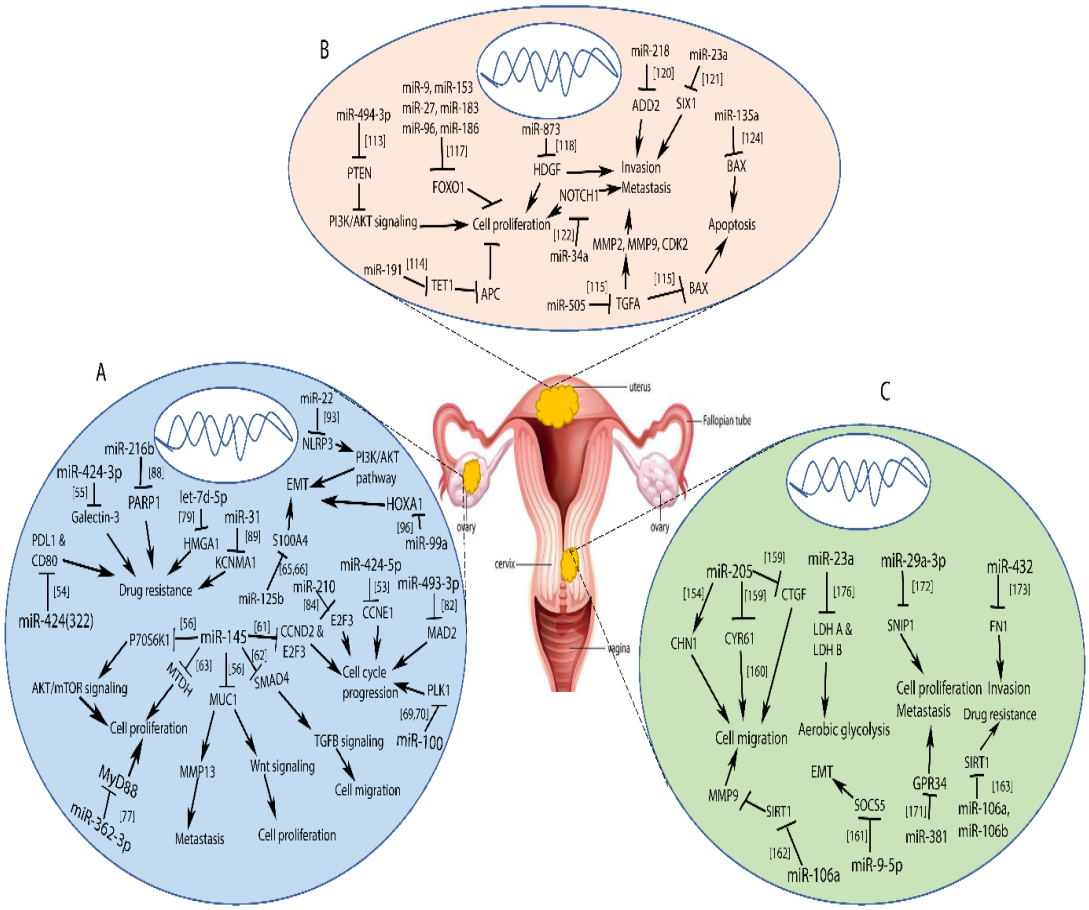

Figure 2. A) Micro RNAs in ovarian cancer: miR-31, let-7d-5p, miR-216b, miR-424-3p and miR-424(322) contribute to chemo-resistance of ovarian cancer cells by targeting Potassium-Calcium-Activated Channel Subfamily M Alpha 1, High Mobility Group AT-Hook 1, Poly (ADP-Ribose) Polymerase 1, Galectin-3 and Programmed death-ligand 1/ CD80 Molecule, respectively. The process of epithelial to mesenchymal transition has been regulated by miR-125b, miR-22 and miR-99a by targeting S100 Calcium Binding Protein A4, NLR family, pyrin domain containing 3 and Homeobox A1, respectively. miR-100, miR-493-3p, miR-424-5p, miR-210 and miR-145 were involved in the regulation of cell cycle progression by targeting Polo-Like Kinase 1, Mitotic arrest deficient 2, Cyclin E1, E2F Transcription factor 3 and Cyclin D2/ E2F Transcription factor 3 respectively. miR-145 regulates cell proliferation, migration and metastasis by targeting different genes such as P70S6K1, Metadherin, Mucin 1 and SMAD Family Member 4, B) Micro RNAs in endometrial cancer: miR-9, miR-27, miR-96, miR-153, miR-183 and miR-186 regulated proliferation of endometrial cancer cells by targeting FOXO1. In addition, miR-494-3p, miR-191, miR-34a and miR-873 also regulated cell proliferation by targeting Phosphatase and tensin homolog, Tet Methylcytosine Dioxygenase 1, NOTCH1and Hepatoma-derived growth factor respectively. miR-34a regulated tumor cell metastasis in a NOTCH1 dependent mechanism, whereas, miR-505 regulates metastasis in a Transforming Growth Factor Alpha - Matrix metalloproteinase-1/-9 axis. miR-505 indirectly and miR-135a directly target BAX and then regulate apoptosis. miR-218 and miR-23a regulate cell invasion by targeting Adducin 2 and SIX Homeobox 1, respectively, and C) Micro RNAs in cervical cancer: miR-205 is involved in the regulation of cervical cancer cell migration by promoting the expression of Chimerin 1 and by inhibiting Cysteine-rich angiogenic inducer 61 and Connective tissue growth factor genes. miR-106a contributes to cell migration by modulating the levels of Matrix Metallopeptidase 9 in a Sirtuin 1 dependent mechanism. miR-9-5p regulated the process of epithelial to mesenchymal transition by targeting Suppressor of cytokine signaling 5 gene. miR-29a-3p contributes to cell proliferation by targeting Smad Nuclear Interacting Protein 1 and miR-23a modulated aerobic glycolysis by targeting Lactate dehydrogenase A and B genes. miR-432 regulates cell invasion by targeting Fibronectin 1, while miR-381 regulates metastasis by targeting G Protein-Coupled Receptor 34 gene. miR-106a & b contribute to cisplatin resistance by targeting Sirtuin 1.

3.5 miRNAs in Prostate Cancer

With 1.3 million new cases being reported in 2018, prostate cancer is the second most common cancer among men[8]. Being asymptomatic at an early stage[125,126], late-stage presentation of prostate cancer continues to remain as a challenge in its diagnosis and treatment. Though Prostate-Specific Antigen (PSA) blood test is performed as a routine diagnostic approach for prostate cancer[127,128], the PSA levels were found to be normal in about 15% of the prostate cancer patients[129]. A correlation between prostate cancer progression and its dependence on androgen level was first described by Huggins and Hodgens based on their finding that castration significantly reduced tumor progression in prostate cancer patients. Since then, Androgen Deprivation Therapy (ADT) is the most common treatment used for symptomatic metastatic cancer patients[130]. However, later studies have shown that it aggravated the problems associated with metastatic disease such as osteoporosis, anemia, muscle wasting, and depression in prostate cancer patients[131]. Recent studies have brought some new insights into miRNAs as an alternate diagnostic and therapeutic target for sensitive screening and proper management of prostate cancer (Figure 3).

miR-346, miR-361-3p and miR-197 were identified as modulators of Androgen Receptor (AR) gene expression on screening prostate cancer cells using miR inhibitor library[132]. Unlike the conventional mode of action, they enhance the stability of AR target by binding to its 3'UTR and thereby facilitate tumor migration and invasion[132]. Inhibition of these miRNA could have additive effects when used in combination with anti-androgens for the treatment of prostate cancer[132]. miR-26a acts as a suppressor of Extracellular Vesicle (EV) secretion associated with prostate cancer by targeting SHC4, PFDN4, and CHORDC1, opening the possibility of yet another novel therapeutic approach by inhibiting EV biogenesis to prevent cell proliferation and cell to cell communication[133].

Jan C Brase and his group have suggested circulating miRNAs, particularly miR-375 and miR-141, as promising candidates for novel therapeutic strategies in prostate cancer patients[134]. The levels of miR-375 were found to be upregulated in patient samples with systemic prostate cancer disease than with the primary prostate cancer[134]. miR-141 has also been reported to have higher abundance in high grade tumors than in intermediate risk tumors and low-grade tumors[134,135]. In another study, higher expression of miR-141 has been correlated with adverse disease condition and biochemical recurrence of prostate cancer[136]. However, the functional role of miR-375 and miR-141 in prostate cancer is not yet elucidated. miR-27a was also found to be highly up-regulated in

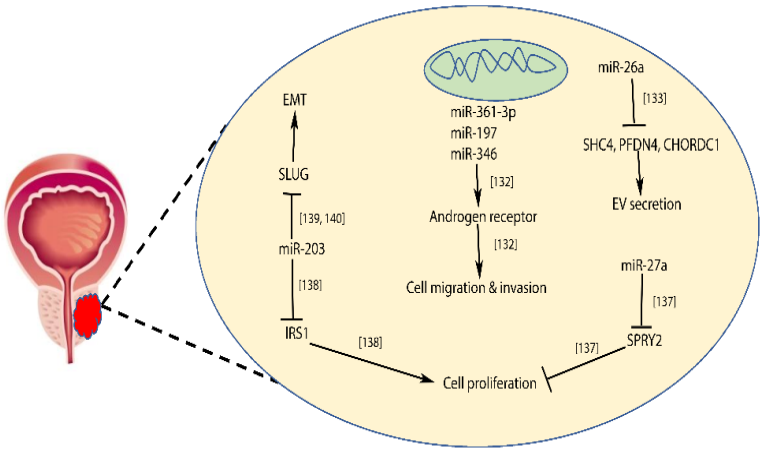

Figure 3. Micro-RNAs in prostate cancer**:** miR-361-3p, miR-197 and miR-346 promoted the expression of Androgen Receptor and thereby cell migration and invasion in prostate cancer. miR-203 contributed to cell proliferation and epithelial to mesenchymal transition by targeting Insulin Receptor Substrate 1 and Slug, respectively. miR-27a has also been implicated in regulating cell proliferation by targeting SPRY2 gene. miR-26a modulated the secretion of extracellular vesicles by targeting genes including SHC Adaptor Protein 4, Prefoldin Subunit 4 and Cysteine- and Histidine-rich domain containing 1.

prostate cancer cells promoting proliferation in a sprouty2 (SPRY2)-dependent manner[137].

miR-203 was found to be an inhibitor of proliferation in prostate cancer cells in an IRS1-dependent manner by blocking ERK pathway[138]. miR-203 could also possibly play a key role in preventing EMT associated with prostate cancer[138] as its direct target include Slug, a metastasis related gene[139,140]. miRNAs such as miR-711[141] and miR-221-5p[142] are reported to act as tumor suppressor in prostate cancer by two independent studies, but their function is not well characterised.

A holistic approach by Verma *et al*. had made it possible to identify dysregulation of miRNAs across various stages of prostate cancer progression using representative cell lines for each stage. The stages were categorised into three: i) early stage androgen sensitivity, ii) advanced stage with loss of androgen receptor function, and iii) Castration-Resistant Prostate Cancer (CRPC) having repressed androgen receptor[143]. miR-146 was reported to be highly up-regulated in advanced stage of prostate cancer with PTGS2 as its prime target[143]. At early stage and CRPC, miR-146, was reported to bind 3'UTR of EGFR[143]. miR-17 was reported to be significantly up-regulated, while miR-205, miR-221, and let-7-g were down-regulated irrespective of the stages of prostate cancer. Different expression levels of various miRNAs have resulted in a patterned expression of their target, AGO2, an upstream transcriptional regulator associated with prostate cancer progression[143,144]. AGO2 was reported to be inactive during early and CRPC stage, while active in advanced stage of prostate cancer[143].

Undoubtedly, the field of prostate cancer research has contributed quite a lot to a better understanding of the disease progression. However, the research focussing on the regulatory effects of miRNAs in prostate cancer in a therapeutic point of view must be encouraged.

3.6 miRNAs in Cervical Cancer

Cervical Cancer (CC) is reported to be the fourth common form of cancer in female population worldwide with an estimated mortality of about 54% of the total cases diagnosed with the disease in 2018[144]. Chronic Human Papilloma Virus (HPV) infection is considered to be a major factor causing invasive cervical cancer[145]. Though 70% of all cervical cancer cases in the world is due to HPV types 16 and 18[146], other factors like prolonged use of oral contraceptives could act as cofactors to HPV leading to cervical and pre-cancer[147]. One of the most devastating aspects of cervical cancer is the early progression of its primary tumor into metastasis creating a major challenge in prognosis and treatment of the disease[148-151]. Patients with locally advanced cervical cancer often exhibit lymph node metastases, particularly at orbituator and medial external ilac nodes[152]. Currently, lymphatic metastasis is mainly diagnosed using imaging technology such as CT and MRI and thereby determining the size of the lymphatic node in cervical cancer patients, but there lies ambiguity as there is lack of sensitivity associated with it[153]. Recent studies have thrown light over miRNAs that play a key role in invasion and lymph node metastasis of cervical cancer. For the first time, Liu *et al*. have reported miR-205 to be a positive regulator of the lymph node metastasis in a1-chimaerin (CHN1)-dependent manner leading to aggressive cervical cancer progression[154].

Surprisingly, miR-205 was found to be a direct positive regulator of CHN1. However, the mechanism behind the positive regulation exhibited by some of the miRNAs is not yet clear[154-157]. Based on the results from colocalization studies *in situ*, CHN1 is suggested to be a regulator of F-actin, a key cytoskeletal component that facilitates cell migration[154,158].

Other major targets of miR-205 include CYR61 and CTGF, which also promotes metastasis of cervical cancer[159]. Both CYR61 and CTGF, belonging to cysteine-rich 16/connective tissue growth factor/nephroblastoma family, promote cell migration[160]. miR-205 could possibly be developed into a biomarker for detecting locally advanced metastases in cervical cancer.

Wei *et al.*, has reported that a higher level of miR9-5p was often associated with cervical cancer patients positive for lymph nodes than those with negative lymph nodes[161]. miR-9-5p has been found to induce EMT by targeting SOCS5 and bring about tumor progression in cervical cancer[161]. Edatt *et al.*, have reported that miR-106a regulates cell migration *in vitro* by modulating the levels of MMP9 in a SIRT1-dependent mechanism[162]. In addition, Raji *et al.*, have reported that miR-106a/b contributes to chemoresistance of HeLa cells by targeting SIRT1[163].

miR-21 is yet another miRNA found to be oncogenic in most of the human cancers, including cervical cancer. However, the molecular mechanism of its action is not yet clear[164-167]. Recent studies have elucidated its role in EMT in a ZEB1 dependent manner though ZEB1 is not a direct target of miR-21[168]. Circulating miR-21 has also been reported as an indicator of lymph node metastasis

of cervical cancer, acting along miR-21/RASA1 axis inducing EMT[165], in which RASA1 is a known inhibitor of Ras protein[169]. But, high levels of circulating miR-21 are correlated with bad prognosis and shorter survival time in cervical cancer patients[165].

Another miRNA, miR-221-3p, has been reported to be a clinically important promoter of lymphatic metastasis in cervical cancer patients[170]. TWIST2-induced miR-221-3p acts in a THBS2-dependent manner in accelerating invasion in cervical cancer patients[170]. But it is necessary to conduct deep study in order to understand TWIST2/miR221-3p/THBS2 network completely[170] to develop potential therapeutic to prevent CC progression.

miRNAs that play an inhibitory role by preventing the invasion and metastasis of cervical cancer have also been identified. miR-381 was found to be significantly down-regulated in the cervical cancer cell lines[171]. G-protein coupled receptor GPR34, a direct target of miR-381, is often up-regulated in cervical cell lines promoting its progression and metastasis[171]. miR-29a-3p was found to be inhibiting the proliferation and metastasis of cervical cancer cell lines in a Smad nuclear interacting protein 1 (SNIP1)-dependent manner[172], while miR-432 did the same in a fibronectin1 (FN1)-dependent manner. Decreased miR-432 expression was found to be associated with lymph node metastasis[173]. However, the roles of miR-381 and miR-29a3p in lymph node metastasis have not yet been elucidated.

miR-143 has been suggested as a biomarker of lymph node metastasis before proceeding for a surgery in cervical cancer patients[174]. miR-143, located in chromosome 5 (5q32), is close to HPV16 integration site[175], which might interfere with the formation of precursor miR-143 resulting in its lower expression in HPV16 positive CSC patients[174]. miR-143 was found to be significantly down-regulated in Cervical Squamous Cancer (CSC) patients with lymph node metastasis than without lymph node metastasis[174]. A negative correlation between miR-143 expression and tumor size in the context of cervical cancer has also been reported[174]. Aerobic glycolysis has been considered as one of the key hall-marks of cancer and in HeLa cells, miR-23a has been reported to be contributing to that by targeting LDH A and LDH B genes[176].

Lymph node metastasis-specific miRNAs and their target genes associated with cervical cancer progression have also been predicted using a cox-proportional hazard regression model and *in silico* tools such as miRDB and Targetscan[177]. The model suggests four miRNAs, namely, miR-502, miR-145, miR-142, and miR-33b, and seven target genes -CXCL12, IGF1, PTPRC, CDH5, RAD51B, REV3L, and WDHD1, to be the key role-players in lymph node metastasis in cervical cancer patients. Though the levels of miR-145 were consistent with experimental conditions[178], the levels of miR-142 contradicted with that of experimental results[179]. Similarly, the expression of genes CXCL12[180], IGF1, WDHD1[181-185] and RAD51B[186,187] correlated with that of experiments conducted in cervical cancer cell lines; however, their profound role in lymph node metastasis remains to be validated. The levels of REV3L under experimental conditions[188,189] contradicted the predicted result from the model. The role of miR-502, miR-33b, PTPRC and CDH5 are yet to be identified in the context of cervical cancer[177]. Though the prediction model opens up possibilities of developing novel biomarkers or therapeutic targets to prevent early metastasis, there is a need for experimental validation in physiological context of cervical cancer cell lines.

4. Conclusion

miRNAs associated with endocrine-dependent malignancies of human reproductive system could be oncogenic or suppressive in nature. Thus, miRNAs present themselves as promising candidates for the prognosis and treatment of human reproductive system associated malignancies. Research till date has helped to identify circulating miRNAs in the serum or in extracellular vesicles, which would serve as biomarkers. However, the functional roles of certain miRNAs have not yet been determined. Therefore, in-depth study is required to understand the molecular mechanism of these miRNAs in the context of endocrine-dependent malignancies.

5. References

1. O'Brien J, Hayder H, Zayed Y, Peng C. Overview of microRNA biogenesis, mechanisms of actions, and circulation. Front Endocrinol (Lausanne). 2018; 9:402. https://doi.org/10.3389/fendo.2018.00402. PMid:30123182 PMCid:PMC6085463.
2. Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell. 2005; 120(1):15-20. https://doi.org/10.1016/j.cell.2004.12.035. PMid:15652477.
3. Cook MS, Blelloch R. Small RNAs in germline development. Curr Top Dev Biol. 2013; 102:159-205.

https://doi.org/10.1016/B978-0-12-416024-8.00006-4. PMid:23287033.

4. Hayashi K, Chuva de Sousa Lopes SM, Kaneda M, *et al*. MicroRNA biogenesis is required for mouse primordial germ cell development and spermatogenesis. PLoS One. 2008; 3(3):e1738. https://doi.org/10.1371/journal.pone.0001738. PMid:18320056 PMCid:PMC2254191.
5. Hong X, Luense LJ, McGinnis LK, Nothnick WB, Christenson LK. Dicer1 is essential for female fertility and normal development of the female reproductive system. Endocrinology. 2008; 149(12):6207-12. https://doi.org/10.1210/en.2008-0294. PMid:18703631 PMCid:PMC2613048.
6. Liu W, Niu Z, Li Q, Pang RT, Chiu PC, Yeung WS. MicroRNA and embryo implantation. Am J Reprod Immunol. 2016; 75(3):263-271. https://doi.org/10.1111/aji.12470. PMid:26707514.
7. Kozieł MJ, Kowalska K, Piastowska-Ciesielska AW. Claudins: New players in human fertility and reproductive system cancers. Cancers (Basel). 2020; 12(3):711. https://doi.org/10.3390/cancers12030711. PMid:32197343 PMCid:PMC7140004.
8. Bray F, Ferlay J, Soerjomataram I, *et al*. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. [published correction appears in CA Cancer J Clin. 2020; 70(4):313]. CA Cancer J Clin. 2018; 68(6):394-424. https://doi.org/10.3322/caac.21492. PMid:30207593.
9. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019; 69(1):7-34. https://doi.org/10.3322/caac.21551. PMid:30620402.
10. Hecht JL, Mutter GL. Molecular and pathologic aspects of endometrial carcinogenesis. J Clin Oncol. 2006; 24(29):4783-4791. https://doi.org/10.1200/JCO.2006.06.7173. PMid:17028294.
11. Rodriguez A, Griffiths-Jones S, Ashurst JL, Bradley A. Identification of mammalian microRNA host genes and transcription units. Genome Res. 2004; 14(10A):1902-1910. https://doi.org/10.1101/gr.2722704. PMid:15364901 PMCid:PMC524413.
12. Saini HK, Griffiths-Jones S, Enright AJ. Genomic analysis of human microRNA transcripts. Proc Natl Acad Sci USA. 2007; 104(45):17719-17724. https://doi.org/10.1073/pnas.0703890104. PMid:17965236 PMCid:PMC2077053.
13. Borchert GM, Lanier W, Davidson BL. RNA polymerase III transcribes human microRNAs. Nat Struct Mol Biol. 2006; 13(12):1097-1101. https://doi.org/10.1038/nsmb1167. PMid:17099701.
14. Davis BN, Hilyard AC, Nguyen PH, Lagna G, Hata A. Smad proteins bind a conserved RNA sequence to promote microRNA maturation by Drosha. Mol Cell. 2010; 39(3):373-384. https://doi.org/10.1016/j.molcel.2010.07.011. PMid:20705240 PMCid:PMC2921543.
15. Denli AM, Tops BB, Plasterk RH, Ketting RF, Hannon GJ. Processing of primary microRNAs by the Microprocessor complex. Nature. 2004; 432(7014):231-235. https://doi.org/10.1038/nature03049. PMid:15531879.
16. Bohnsack MT, Czaplinski K, Gorlich D. Exportin 5 is a RanGTP-dependent dsRNA-binding protein that mediates nuclear export of pre-miRNAs. RNA. 2004; 10(2):185-191. https://doi.org/10.1261/rna.5167604. PMid:14730017 PMCid:PMC1370530.
17. Haase AD, Jaskiewicz L, Zhang H, *et al*. TRBP, a regulator of cellular PKR and HIV-1 virus expression, interacts with Dicer and functions in RNA silencing. EMBO Rep. 2005; 6(10):961-967. https://doi.org/10.1038/sj.embor.7400509. PMid:16142218 PMCid:PMC1369185.
18. Zhang H, Kolb FA, Brondani V, Billy E, Filipowicz W. Human Dicer preferentially cleaves dsRNAs at their termini without a requirement for ATP. EMBO J. 2002; 21(21):5875-85. https://doi.org/10.1093/emboj/cdf582. PMid:12411505 PMCid:PMC131079.
19. Kim VN. MicroRNA biogenesis: coordinated cropping and dicing. Nat Rev Mol Cell Biol. 2005; 6(5):376-385. https://doi.org/10.1038/nrm1644. PMid:15852042.
20. Ha M, Kim VN. Regulation of microRNA biogenesis. Nat Rev Mol Cell Biol. 2014; 15(8):509-524. https://doi.org/10.1038/nrm3838. PMid:25027649.
21. Ellwanger DC, Büttner FA, Mewes HW, Stümpflen V. The sufficient minimal set of miRNA seed types. Bioinformatics. 2011; 27(10):1346-1350. https://doi.org/10.1093/bioinformatics/btr149. PMid:21441577 PMCid:PMC3087955.
22. Huntzinger E, Izaurralde E. Gene silencing by microRNAs: contributions of translational repression and mRNA decay. Nat Rev Genet. 2011; 12(2):99-110. https://doi.org/10.1038/nrg2936. PMid:21245828.
23. Liu J, Valencia-Sanchez MA, Hannon GJ, Parker R. MicroRNA-dependent localization of targeted mRNAs to mammalian P-bodies. Nat Cell Biol. 2005; 7(7):719-723. https://doi.org/10.1038/ncb1274. PMid:15937477 PMCid:PMC1855297.
24. Subramani R, Nandy SB, Pedroza DA, Lakshmanaswamy R. Role of Growth Hormone in Breast Cancer. Endocrinology. 2017; 158(6):1543-1555. https://doi.org/10.1210/en.2016-1928. PMid:28379395.
25. Chung SH. Targeting female hormone receptors as cervical cancer therapy. Trends Endocrinol Metab. 2015; 26(8):399-401. https://doi.org/10.1016/j.tem.2015.06.004. PMid:26163756 PMCid:PMC4526440.
26. Richter E., Srivastava S., Dobi A. Androgen receptor and prostate cancer. Prostate Cancer Prostatic Dis. 2007;

10:114-118. https://doi.org/10.1038/sj.pcan.4500936. PMid:17297502.

27. So WK, Cheng JC, Poon SL, Leung PC. Gonadotropin-releasing hormone and ovarian cancer: a functional and mechanistic overview. FEBS J. 2008; 275(22):5496-5511. https://doi.org/10.1111/j.1742-4658.2008.06679.x. PMid:18959739.
28. Wetendorf M, Li R, Wu SP, *et al*. Constitutive expression of progesterone receptor isoforms promotes the development of hormone-dependent ovarian neoplasms. Sci Signal. 2020; 13(652):eaaz9646. https://doi.org/10.1126/scisignal.aaz9646. PMid:33023986.
29. Murphy CG, Dickler MN. Endocrine resistance in hormone-responsive breast cancer: mechanisms and therapeutic strategies. EndocrRelat Cancer. 2016; 23(8):R337-R352. https://doi.org/10.1530/ERC-16-0121. PMid:27406875.
30. Ye ZB, Ma G, Zhao YH, *et al*. miR-429 inhibits migration and invasion of breast cancer cells in vitro. Int J Oncol. 2015; 46(2):531-538. https://doi.org/10.3892/ijo.2014.2759. PMid:25405387 PMCid:PMC4277243.
31. Wei YT, Guo DW, Hou XZ, Jiang DQ. miRNA-223 suppresses FOXO1 and functions as a potential tumor marker in breast cancer. Cell Mol Biol (Noisy-le-grand). 2017; 20; 63(5):113-118. https://doi.org/10.14715/cmb/2017.63.5.21. PMid:28719355.
32. Gravgaard KH, Lyng MB, Laenkholm AV, *et al*. The miRNA-200 family and miRNA-9 exhibit differential expression in primary versus corresponding metastatic tissue in breast cancer. Breast Cancer Res Treat. 2012; 134(1):207-217. https://doi.org/10.1007/s10549-012-1969-9. PMid:22294488.
33. Ma L, Young J, Prabhala H, *et al*. miR-9, a MYC/MYCN-activated microRNA, regulates E-cadherin and cancer metastasis. Nat Cell Biol. 2010; 12(3):247-256. https://doi.org/10.1038/ncb2024. PMid:20173740 PMCid:PMC2845545.
34. Liu DZ, Chang B, Li XD, Zhang QH, Zou YH. MicroRNA-9 promotes the proliferation, migration, and invasion of breast cancer cells via down-regulating FOXO1. Clin Transl Oncol. 2017; 19(9):1133-1140. https://doi.org/10.1007/s12094-017-1650-1. PMid:28397066.
35. Li X, Zeng Z, Wang J, *et al*. MicroRNA-9 and breast cancer. Biomed Pharmacother. 2020; 122:109687. https://doi.org/10.1016/j.biopha.2019.109687. PMid:31918267.
36. Fong MY, Zhou W, Liu L, *et al*. Breast-cancer-secreted miR-122 reprograms glucose metabolism in premetastatic niche to promote metastasis. Nat Cell Biol. 2015; 17(2):183-194. https://doi.org/10.1038/ncb3094. PMid:25621950 PMCid:PMC4380143.
37. Zhao H, Kang X, Xia X, *et al*. miR-145 suppresses breast cancer cell migration by targeting FSCN-1 and inhibiting epithelial-mesenchymal transition. (Published 2016 Jul 15). Am J Transl Res. 2016; 8(7):3106-3114.
38. Li P, Sheng C, Huang L, *et al*. Tangcluster is up-regulated in most breast cancers and increases cell proliferation and migration (Published 2014 Nov 14). Breast Cancer Res. 2014; 16(6):473. https://doi.org/10.1186/s13058-014-0473-z. PMid:25394902 PMCid:PMC4303194.
39. Wu T, Song H, Xie D, *et al*. Mir-30b-5p promotes proliferation, migration, and invasion of breast cancer cells via targeting ASPP2. Biomed Res Int. 2020; 2020:7907269. https://doi.org/10.1155/2020/7907269. PMid:32420372 PMCid:PMC7210518.
40. Hannafon BN, Cai A, Calloway CL, *et al*. miR-23b and miR-27b are oncogenic microRNAs in breast cancer: evidence from a CRISPR/Cas9 deletion study. BMC Cancer. 2019; 19(1):642. https://doi.org/10.1186/s12885-019-5839-2. PMid:31253120 PMCid:PMC6599331.
41. Liang L, Fu J, Wang S, *et al*. MiR-142-3p enhances chemosensitivity of breast cancer cells and inhibits autophagy by targeting HMGB1. Acta Pharm Sin B. 2020; 10(6):1036-1046. https://doi.org/10.1016/j.apsb.2019.11.009. PMid:32642410 PMCid:PMC7332808.
42. Qiu C, Huang F, Zhang Q, Chen W, Zhang H. miR-205-3p promotes proliferation and reduces apoptosis of breast cancer MCF-7 cells and is associated with poor prognosis of breast cancer patients. J Clin Lab Anal. 2019; 33(8):e22966. https://doi.org/10.1002/jcla.22966.
43. Nair MG, Prabhu JS, Korlimarla A, *et al*. miR-18a activates Wnt pathway in ER-positive breast cancer and is associated with poor prognosis. Cancer Med. 2020; 9(15):5587-5597. https://doi.org/10.1002/cam4.3183. PMid:32543775 PMCid:PMC7402845.
44. Pan Y, Jiao G, Wang C, Yang J, Yang W. MicroRNA-421 inhibits breast cancer metastasis by targeting metastasis associated 1. Biomed Pharmacother. 2016; 83:1398-1406. https://doi.org/10.1016/j.biopha.2016.08.058. PMid:27583980.
45. Sharma S, Nagpal N, Ghosh PC, Kulshreshtha R. P53-miR-191-SOX4 regulatory loop affects apoptosis in breast cancer. RNA. 2017; 23(8):1237-1246. https://doi.org/10.1261/rna.060657.117. PMid:28450532 PMCid:PMC5513068.
46. Zhang H, Peng J, Lai J, *et al*. MiR-940 promotes malignant progression of breast cancer by regulating FOXO3. Biosci Rep. 2020; 40(9):BSR20201337. https://doi.org/10.1042/BSR20201337. PMid:32840296 PMCid:PMC7494982.
47. Wang H, Tan Z, Hu H, *et al*. microRNA-21 promotes breast cancer proliferation and metastasis by targeting LZTFL1. BMC Cancer. 2019; 19(1):738. https://doi.org/10.1186/s12885-019-5951-3. PMid:31351450 PMCid:PMC6661096.
48. Yan LX, Wu QN, Zhang Y, *et al*. Knockdown of miR-21 in human breast cancer cell lines inhibits proliferation, in

vitro migration and in vivo tumor growth. Breast Cancer Res. 2011; 13(1):R2. https://doi.org/10.1186/bcr2803. PMid:21219636 PMCid:PMC3109565.

49. Cai WL, Huang WD, Li B, *et al*. microRNA-124 inhibits bone metastasis of breast cancer by repressing Interleukin-11 [published correction appears in Mol Cancer. 2020 Jun 27; 19(1):111]. Mol Cancer. 2018; 17(1):9. https://doi.org/10.1186/s12943-017-0746-0. PMid:29343249 PMCid:PMC5773190.
50. Han S, Zou H, Lee JW, *et al*. miR-1307-3p stimulates breast cancer development and progression by targeting SMYD4. J Cancer. 2019; 10(2):441-448. https://doi.org/10.7150/jca.30041. PMid:30719138 PMCid:PMC6360296.
51. Chen YN, Ren CC, Yang L, *et al*. MicroRNA let-7d-5p rescues ovarian cancer cell apoptosis and restores chemosensitivity by regulating the p53 signalling pathway via HMGA1. Int J Oncol. 2019; 54(5):1771-1784. https://doi.org/10.3892/ijo.2019.4731.
52. Iorio MV, Visone R, Di Leva G, *et al*. MicroRNA signatures in human ovarian cancer. Cancer Res. 2007; 67(18):8699-8707. https://doi.org/10.1158/0008-5472.CAN-07-1936. PMid:17875710.
53. Liu J, Gu Z, Tang Y, *et al*. Tumour-suppressive microRNA-424-5p directly targets CCNE1 as potential prognostic markers in epithelial ovarian cancer. Cell Cycle. 2018; 17(3):309-318. https://doi.org/10.1080/15384101.2017.1407894. PMid:29228869 PMCid:PMC5914728.
54. Xu S, Tao Z, Hai B, *et al*. miR-424(322) reverses chemoresistance via T-cell immune response activation by blocking the PD-L1 immune checkpoint. Nat Commun. 2016; 7:11406. Published 2016 May 5. https://doi.org/10.1038/ncomms11406. PMid:27147225 PMCid:PMC4858750.
55. Bieg D, Sypniewski D, Nowak E, Bednarek I. MiR-424-3p suppresses galectin-3 expression and sensitizes ovarian cancer cells to cisplatin. Arch Gynecol Obstet. 2019; 299(4):1077-1087. https://doi.org/10.1007/s00404-018-4999-7. PMid:30585294 PMCid:PMC6435611.
56. Wu H, Xiao Z, Wang K, Liu W, Hao Q. MiR-145 is downregulated in human ovarian cancer and modulates cell growth and invasion by targeting p70S6K1 and MUC1. Biochem Biophys Res Commun. 2013; 441(4):693-700. https://doi.org/10.1016/j.bbrc.2013.10.053. PMid:24157791.
57. Gao N, Flynn DC, Zhang Z, *et al*. G1 cell cycle progression and the expression of G1 cyclins are regulated by PI3K/AKT/mTOR/p70S6K1 signalling in human ovarian cancer cells. Am J Physiol Cell Physiol. 2004; 287(2):C281-C291. https://doi.org/10.1152/ajpcell.00422.2003. PMid:15028555.
58. Ye Q, Yan Z, Liao X, *et al*. MUC1 induces metastasis in esophageal squamous cell carcinoma by upregulating matrix metalloproteinase 13. Lab Invest. 2011; 91(5):778-787. https://doi.org/10.1038/labinvest.2011.12. PMid:21339746.
59. Huang L, Ren J, Chen D, Li Y, Kharbanda S, Kufe D. MUC1 cytoplasmic domain coactivates Wnt target gene transcription and confers transformation. Cancer Biol Ther. 2003; 2(6):702-706. https://doi.org/10.4161/cbt.2.6.610.
60. Sheng Q, Zhang Y, Wang Z, *et al*. Cisplatin-mediated down-regulation of miR-145 contributes to up-regulation of PD-L1 via the c-Myc transcription factor in cisplatin-resistant ovarian carcinoma cells. Clin Exp Immunol. 2020; 200(1):45-52. https://doi.org/10.1111/cei.13406. PMid:31821542.
61. Hua M, Qin Y, Sheng M, *et al*. miR 145 suppresses ovarian cancer progression via modulation of cell growth and invasion by targeting CCND2 and E2F3. Mol Med Rep. 2019; 19(5):3575-3583. https://doi.org/10.3892/mmr.2019.10004.
62. Zhou J, Zhang X, Li W, Chen Y. MicroRNA-145-5p regulates the proliferation of epithelial ovarian cancer cells via targeting SMAD4. J Ovarian Res. 2020; 13(1):54. https://doi.org/10.1186/s13048-020-00656-1. PMid:32366274 PMCid:PMC7199349.
63. Dong R, Liu X, Zhang Q, *et al*. miR-145 inhibits tumor growth and metastasis by targeting metadherin in high-grade serous ovarian carcinoma. Oncotarget. 2014; 5(21):10816-10829. https://doi.org/10.18632/oncotarget.2522. PMid:25333261 PMCid:PMC4279412.
64. Luo S, Wang J, Ma Y, Yao Z, Pan H. PPARγ inhibits ovarian cancer cells proliferation through upregulation of miR-125b. Biochem Biophys Res Commun. 2015; 462(2):85-90. https://doi.org/10.1016/j.bbrc.2015.04.023. PMid:25944662.
65. Bi YN, Guan JP, Wang L, Li P, Yang FX. Clinical significance of microRNA-125b and its contribution to ovarian carcinogenesis. Bioengineered. 2020; 11(1):939-948. https://doi.org/10.1080/21655979.2020.1814660. PMid:32842846.
66. Ying X, Wei K, Lin Z, *et al*. MicroRNA-125b suppresses ovarian cancer progression via suppression of the epithelial-mesenchymal tTransition pathway by targeting the SET protein. Cell Physiol Biochem. 2016; 39(2):501-10. https://doi.org/10.1159/000445642. PMid:27383536.
67. Zhang D, Guo H, Feng W, Qiu H. LAMC2 regulated by microRNA-125a-5p accelerates the progression of ovarian cancer via activating p38 MAPK signalling. Life Sci. 2019; 232:116648. https://doi.org/10.1016/j.lfs.2019.116648. PMid:31301414.
68. Kong F, Sun C, Wang Z, *et al*. miR-125b confers resistance of ovarian cancer cells to cisplatin by targeting pro-apoptotic Bcl-2 antagonist killer 1. J Huazhong Univ Sci Technolog

Med Sci. 2011; 31(4):543. https://doi.org/10.1007/s11596-011-0487-z. PMid:21823019.

69. Peng DX, Luo M, Qiu LW, He YL, Wang XF. Prognostic implications of microRNA-100 and its functional roles in human epithelial ovarian cancer. Oncol Rep. 2012; 27(4):1238-1244. https://doi.org/10.3892/or.2012.1625. PMid:22246341 PMCid:PMC3583406.
70. Takaki T, Trenz K, Costanzo V, Petronczki M. Polo-like kinase 1 reaches beyond mitosis-cytokinesis, DNA damage response, and development. Curr Opin Cell Biol. 2008; 20:650-660. https://doi.org/10.1016/j.ceb.2008.10.005. PMid:19000759.
71. Guo P, Xiong X, Zhang S, Peng D. miR-100 resensitizes resistant epithelial ovarian cancer to cisplatin. Oncol Rep. 2016; 36(6):3552-3558. https://doi.org/10.3892/or.2016.5140. PMid:27748936.
72. Nagaraja AK, Creighton CJ, Yu Z, *et al*. A link between mir-100 and FRAP1/mTOR in clear cell ovarian cancer. Mol Endocrinol. 2010; 24(2):447-463. https://doi.org/10.1210/me.2009-0295. PMid:20081105 PMCid:PMC2817607.
73. Tang L, Yang B, Cao X, Li Q, Jiang L, Wang D. MicroRNA-377-3p inhibits growth and invasion through sponging JAG1 in ovarian cancer. Genes Genomics. 2019; 41(8):919-926. https://doi.org/10.1007/s13258-019-00822-w. PMid:31041680.
74. Yu R, Cai L, Chi Y, Ding X, Wu X. miR-377 targets CUL4A and regulates metastatic capability in ovarian cancer. Int J Mol Med. 2018; 41(6):3147-3156. https://doi.org/10.3892/ijmm.2018.3540.
75. Zhang H, Wang Q, Zhao Q, Di W. MiR-124 inhibits the migration and invasion of ovarian cancer cells by targeting SphK1. J Ovarian Res. 2013; 6(1):84. https://doi.org/10.1186/1757-2215-6-84. PMid:24279510 PMCid:PMC3879084.
76. Yuan L, Li S, Zhou Q, *et al*. MiR-124 inhibits invasion and induces apoptosis of ovarian cancer cells by targeting programmed cell death 6. Oncol Lett. 2017; 14(6):7311-7317. https://doi.org/10.3892/ol.2017.7157.
77. Yuan J, Li T, Yi K, Hou M. The suppressive role of miR-362-3p in epithelial ovarian cancer. Heliyon. 2020; 6(7):e04258. https://doi.org/10.1016/j.heliyon.2020.e04258. PMid:32671239 PMCid:PMC7347651.
78. Tian J, Xu YY, Li L, Hao Q. MiR-490-3p sensitizes ovarian cancer cells to cisplatin by directly targeting ABCC2. Am J Transl Res. 2017; 9(3):1127-1138.
79. Chen SN, Chang R, Lin LT, *et al*. MicroRNA in ovarian cancer: Biology, pathogenesis, and therapeutic opportunities. Int J Environ Res Public Health. 2019; 16(9):1510. https://doi.org/10.3390/ijerph16091510. PMid:31035447 PMCid:PMC6539609.
80. García-Vázquez R, Gallardo Rincón D, Ruiz-García E, *et al*. let-7d-3p is associated with apoptosis and response to neoadjuvant chemotherapy in ovarian cancer. Oncol Rep. 2018; 39(6):3086-3094. https://doi.org/10.3892/or.2018.6366. PMid:29658612.
81. Kleemann M, Schneider H, Unger K, *et al*. Induction of apoptosis in ovarian cancer cells by miR-493-3p directly targeting AKT2, STK38L, HMGA2, ETS1 and E2F5. Cell Mol Life Sci. 2019; 76(3):539-559. https://doi.org/10.1007/s00018-018-2958-x. PMid:30392041.
82. Tambe M, Pruikkonen S, Mäki-Jouppila J, *et al*. Novel Mad2-targeting miR-493-3p controls mitotic fidelity and cancer cells' sensitivity to paclitaxel. Oncotarget. 2016; 7(11):12267-12285. https://doi.org/10.18632/oncotarget.7860. PMid:26943585 PMCid:PMC4914283.
83. Giannakakis A, Sandaltzopoulos R, Greshock J, *et al*. miR-210 links hypoxia with cell cycle regulation and is deleted in human epithelial ovarian cancer. Cancer Biol Ther. 2008; 7(2):255-264. https://doi.org/10.4161/cbt.7.2.5297. PMid:18059191 PMCid:PMC3233968.
84. Jin Y, Wei J, Xu S, Guan F, Yin L, Zhu H. miR-210-3p regulates cell growth and affects cisplatin sensitivity in human ovarian cancer cells via targeting E2F3. Mol Med Rep. 2019; 19(6):4946-4954. https://doi.org/10.3892/mmr.2019.10129.
85. Ding L, Zhao L, Chen W, Liu T, Li Z, Li X. miR-210, a modulator of hypoxia-induced epithelial-mesenchymal transition in ovarian cancer cell. Int J Clin Exp Med. 2015; 8(2):2299-2307.
86. Li L, Huang K, You Y, *et al*. Hypoxia-induced miR-210 in epithelial ovarian cancer enhances cancer cell viability via promoting proliferation and inhibiting apoptosis. Int J Oncol. 2014; 44(6):2111-2120. https://doi.org/10.3892/ijo.2014.2368. PMid:24715221.
87. González-Rodriguez A, Escribano O, Alba J, Rondinone CM, Benito M, Valverde AM. Levels of protein tyrosine phosphatase 1B determine susceptibility to apoptosis in serum-deprived hepatocytes. J Cell Physiol. 2007; 212(1):76-88. https://doi.org/10.1002/jcp.21004. PMid:17323378.
88. Liu Y, Niu Z, Lin X, Tian Y. MiR-216b increases cisplatin sensitivity in ovarian cancer cells by targeting PARP1. Cancer Gene Ther. 2017; 24(5):208-214. https://doi.org/10.1038/cgt.2017.6. PMid:28281524.
89. Samuel P, Pink RC, Caley DP, Currie JM, Brooks SA, Carter DR. Over-expression of miR-31 or loss of KCNMA1 leads to increased cisplatin resistance in ovarian cancer cells. Tumour Biol. 2016; 37(2):2565-2573. https://doi.org/10.1007/s13277-015-4081-z. PMid:26386726.
90. Mitamura T, Watari H, Wang L, *et al*. Downregulation of miRNA-31 induces taxane resistance in ovarian cancer cells through increase of receptor tyrosine kinase MET.

Oncogenesis. 2013; 2(3):e40. https://doi.org/10.1038/oncsis.2013.3. PMid:23552883 PMCid:PMC3641356.

91. Hassan MK, Watari H, Mitamura T, *et al*. P18/Stathmin1 is regulated by miR-31 in ovarian cancer in response to taxane. Oncoscience. 2015; 2(3):294-308. https://doi.org/10.18632/oncoscience.143. PMid:25897432 PMCid:PMC4394135.
92. Sellin ME, Holmfeldt P, Stenmark S, Gullberg M. Op18/Stathmin counteracts the activity of overexpressed tubulin-disrupting proteins in a human leukemia cell line. Exp Cell Res. 2008; 314(6):1367-77. https://doi.org/10.1016/j.yexcr.2007.12.018. PMid:18262179
93. Wu, H., Liu, J., Zhang, Y. *et al*. miR-22 suppresses cell viability and EMT of ovarian cancer cells via NLRP3 and inhibits PI3K/AKT signalling pathway. Clin Transl Oncol. 2020. https://doi.org/10.1007/s12094-020-02413-8. PMid:32524269.
94. Li Y, Gu Y, Tang N, Liu Y, Zhao Z. miR-22-Notch signalling pathway is involved in the regulation of the apoptosis and autophagy in human ovarian cancer cells. Biol Pharm Bull. 2018; 41(8):1237-1242. https://doi.org/10.1248/bpb.b18-00084. PMid:30068873.
95. Chen S, Chen X, Xiu YL, Sun KX, Zhao Y. Inhibition of ovarian epithelial carcinoma tumorigenesis and progression by microRNA 106b mediated through the RhoC pathway. PLoS One. 2015; 10(5):e0125714. https://doi.org/10.1371/journal.pone.0125714. PMid:25933027 PMCid:PMC4416747.
96. Zhang L, Liu XL, Yuan Z, Cui J, Zhang H. MiR-99a suppressed cell proliferation and invasion by directly targeting HOXA1 through regulation of the AKT/mTOR signalling pathway and EMT in ovarian cancer. Eur Rev Med Pharmacol Sci. 2019; 23(11):4663-4672.
97. Laios A, O'Toole S, Flavin R, *et al*. Potential role of miR-9 and miR-223 in recurrent ovarian cancer (Published 2008 Apr 28). Mol Cancer. 2008; 7:35. https://doi.org/10.1186/1476-4598-7-35. PMid:18442408 PMCid:PMC2383925.
98. Sui X, Jiao YN, Yang LH, Liu J. MiR-9 accelerates epithelial-mesenchymal transition of ovarian cancer cells via inhibiting e-cadherin. Eur Rev Med Pharmacol Sci. 2019; 23(3 Suppl):209-216.
99. Sun C, Li N, Yang Z, *et al*. miR-9 regulation of BRCA1 and ovarian cancer sensitivity to cisplatin and PARP inhibition. J Natl Cancer Inst. 2013; 105(22):1750-1758. https://doi.org/10.1093/jnci/djt302. PMid:24168967.
100. Tang H, Yao L, Tao X, *et al*. miR-9 functions as a tumor suppressor in ovarian serous carcinoma by targeting TLN1. Int J Mol Med. 2013; 32(2):381-388. https://doi.org/10.3892/ijmm.2013.1400. PMid:23722670.
101. Zhang L, Zhou Q, Qiu Q, *et al*. CircPLEKHM3 acts as a tumor suppressor through regulation of the miR-9/BRCA1/DNAJB6/KLF4/AKT1 axis in ovarian cancer. Mol Cancer. 2019; 18(1):144. https://doi.org/10.1186/s12943-019-1080-5. PMid:31623606 PMCid:PMC6796346.
102. Li X, Chen W, Zeng W, Wan C, Duan S, Jiang S. microRNA-137 promotes apoptosis in ovarian cancer cells via the regulation of XIAP. Br J Cancer. 2017; 116(1):66-76. https://doi.org/10.1038/bjc.2016.379. PMid:27875524 PMCid:PMC5220146.
103. Eckelman BP, Salvesen GS, Scott FL. Human inhibitor of apoptosis proteins: why XIAP is the black sheep of the family. EMBO Rep. 2006; 7(10):988-994. https://doi.org/10.1038/sj.embor.7400795. PMid:17016456 PMCid:PMC1618369.
104. Sun J, Cai X, Yung MM, *et al*. miR-137 mediates the functional link between c-Myc and EZH2 that regulates cisplatin resistance in ovarian cancer. Oncogene. 2019; 38(4):564-580. https://doi.org/10.1038/s41388-018-0459-x. PMid:30166592 PMCid:PMC7474467.
105. Dong P, Xiong Y, Watari H, *et al*. MiR-137 and miR-34a directly target Snail and inhibit EMT, invasion and sphere-forming ability of ovarian cancer cells. J Exp Clin Cancer Res. 2016; 35(1):132. https://doi.org/10.1186/s13046-016-0415-y. PMid:27596137 PMCid:PMC5011787.
106. Guo J, Xia B, Meng F, Lou G. miR-137 suppresses cell growth in ovarian cancer by targeting AEG-1. Biochem Biophys Res Commun. 2013; 441(2):357-363. https://doi.org/10.1016/j.bbrc.2013.10.052. PMid:24144591.
107. Emdad L, Sarkar D, Su ZZ, *et al*. Astrocyte elevated gene-1: recent insights into a novel gene involved in tumor progression, metastasis and neurodegeneration [published correction appears in Pharmacol Ther. 2007 Jul; 115(1):176]. PharmacolTher. 2007; 114(2):155-170. https://doi.org/10.1016/j.pharmthera.2007.05.001.
108. Hu G, Wei Y, Kang Y. The multifaceted role of MTDH/AEG-1 in cancer progression. Clin Cancer Res. 2009; 15(18):5615-5620. https://doi.org/10.1158/1078-0432.CCR-09-0049. PMid:19723648 PMCid:PMC2747034.
109. He XX, Chang Y, Meng FY, *et al*. MicroRNA-375 targets AEG-1 in hepatocellular carcinoma and suppresses liver cancer cell growth in vitro and in vivo. Oncogene. 2012; 31(28):3357-3369. https://doi.org/10.1038/onc.2011.500. PMid:22056881.
110. Chen W, Du J, Li X, Zhi Z, Jiang S. microRNA-137 downregulates MCL1 in ovarian cancer cells and mediates cisplatin-induced apoptosis. Pharmacogenomics. 2020; 21(3):195-207. https://doi.org/10.2217/pgs-2019-0122. PMid:31967512.
111. Van Sinderen M, Griffiths M, Menkhorst E, *et al*. Restoration of microRNA-29c in type I endometrioid cancer reduced endometrial cancer cell growth. Oncol Lett. 2019; 18(3):2684-2693. https://doi.org/10.3892/ol.2019.10588. PMid:31404303 PMCid:PMC6676720.

112. Felix AS, Weissfeld JL, Stone RA, *et al*. Factors associated with Type I and Type II endometrial cancer. Cancer Causes Control. 2010; 21(11):1851-1856. https://doi.org/10.1007/s10552-010-9612-8. PMid:20628804 PMCid:PMC2962676.
113. Zhu L, Wang X, Wang T, Zhu W, Zhou X. miR 494 3p promotes the progression of endometrial cancer by regulating the PTEN/PI3K/AKT pathway. Mol Med Rep. 2019 Jan; 19(1):581-588. https://doi.org/10.3892/mmr.2018.9649.
114. Yang C, Ota-Kurogi N, Ikeda K, *et al*. MicroRNA-191 regulates endometrial cancer cell growth via TET1-mediated epigenetic modulation of APC. J Biochem. 2020; 168(1):7-14. https://doi.org/10.1093/jb/mvaa014. PMid:32003827.
115. Chen S, Sun KX, Liu BL, Zong ZH, Zhao Y. MicroRNA-505 functions as a tumor suppressor in endometrial cancer by targeting TGF-α. Mol Cancer. 2016; 15:11. https://doi.org/10.1186/s12943-016-0496-4. PMid:26832151 PMCid:PMC4736705.
116. Zhang W, Chen JH, Shan T, *et al*. miR-137 is a tumor suppressor in endometrial cancer and is repressed by DNA hypermethylation. Lab Invest. 2018; 98(11):1397-1407. https://doi.org/10.1038/s41374-018-0092-x. PMid:29955087 PMCid:PMC6214735.
117. Myatt SS, Wang J, Monteiro LJ, *et al*. Definition of microRNAs that repress expression of the tumor suppressor gene FOXO1 in endometrial cancer. Cancer Res. 2010; 70(1):367-377. https://doi.org/10.1158/0008-5472.CAN-09-1891. PMid:20028871 PMCid:PMC2880714.
118. Wang Q, Zhu W. MicroRNA-873 inhibits the proliferation and invasion of endometrial cancer cells by directly targeting hepatoma-derived growth factor. Exp Ther Med. 2019; 18(2):1291-1298. https://doi.org/10.3892/etm.2019.7713.
119. Karaayvaz M, Zhang C, Liang S, *et al*. Prognostic significance of miR-205 in endometrial cancer. PLoS One. 2012; 7(4):e35158. https://doi.org/10.1371/journal.pone.0035158. PMid:22514717 PMCid:PMC3325973.
120. Li XC, Hai JJ, Tan YJ, *et al*. MiR-218 suppresses metastasis and invasion of endometrial cancer via negatively regulating ADD2. Eur Rev Med Pharmacol Sci. 2019; 23(4):1408-1417.
121. Li HL, Sun JJ, Ma H, *et al*. MicroRNA-23a inhibits endometrial cancer cell development by targeting SIX1. Oncol Lett. 2019; 18(4):3792-3802. https://doi.org/10.3892/ol.2019.10694.
122. Wang Z, Wang W, Huang K, *et al*.. MicroRNA-34a inhibits cells proliferation and invasion by down-regulating Notch1 in endometrial cancer. Oncotarget. 2017; 8(67):111258-111270. Published 2017 Nov 30. https://doi.org/10.18632/oncotarget.22770 PMid:29340051 PMCid:PMC5762319.
123. Yanokura M, Banno K, Aoki D. MicroRNA-34b expression enhances chemosensitivity of endometrial cancer cells to paclitaxel. Int J Oncol. 2020; 57(5):1145-1156. Published 2020 Sep 23. https://doi.org/10.3892/ijo.2020.5127. PMid:33300049 PMCid:PMC7549539.
124. Wang J, Zhang L, Jiang W, *et al*. MicroRNA-135a promotes proliferation, migration, invasion and induces chemoresistance of endometrial cancer cells. Eur J Obstet Gynecol Reprod Biol X. 2019; 5:100103. https://doi.org/10.1016/j.eurox.2019.100103. PMid:32021975 PMCid:PMC6994408.
125. Hood SP, Cosma G, Foulds GA, *et al*. Identifying prostate cancer and its clinical risk in asymptomatic men using machine learning of high dimensional peripheral blood flow cytometric natural killer cell subset phenotyping data. Elife. 2020; 9:e50936. Published 2020 Jul 28. https://doi.org/10.7554/eLife.50936. PMid:32717179 PMCid:PMC7386909.
126. Mazhar D, Waxman J. Prostate cancer. Postgrad Med J. 2002; 78(924):590-595. https://doi.org/10.1136/pmj.78.924.590. PMid:12415080 PMCid:PMC1742511.
127. Catalona WJ, Smith DS, Ratliff TL, *et al*. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer [published correction appears in N Engl J Med 1991 Oct 31; 325(18):1324]. N Engl J Med. 1991; 324(17):1156-1161. https://doi.org/10.1056/NEJM199104253241702. PMid:1707140.
128. Hankey BF, Feuer EJ, Clegg LX, *et al*. Cancer surveillance series: interpreting trends in prostate cancer--part I: Evidence of the effects of screening in recent prostate cancer incidence, mortality, and survival rates. J Natl Cancer Inst. 1999; 91(12):1017-1024. https://doi.org/10.1093/jnci/91.12.1017. PMid:10379964.
129. Thompson IM, Pauler DK, Goodman PJ, *et al*. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter [published correction appears in N Engl J Med. 2004 Sep 30; 351(14):1470]. N Engl J Med. 2004; 350(22):2239-2246. https://doi.org/10.1056/NEJMoa031918. PMid:15163773.
130. Huggins C, Hodges CV. Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. J Urol. 2002; 168(1):9-12. https://doi.org/10.1016/S0022-5347(05)64820-3.
131. Perlmutter MA, Lepor H. Androgen deprivation therapy in the treatment of advanced prostate cancer. Rev Urol. 2007; 9 Suppl 1(Suppl 1):S3-S8.
132. Fletcher CE, Sulpice E, Combe S, *et al*. Androgen receptor-modulatory microRNAs provide insight into therapy

resistance and therapeutic targets in advanced prostate cancer. Oncogene. 2019; 38(28):5700-5724. https://doi.org/10.1038/s41388-019-0823-5. PMid:31043708 PMCid:PMC6755970.

133. Urabe F, Kosaka N, Sawa Y, *et al*. miR-26a regulates extracellular vesicle secretion from prostate cancer cells via targeting SHC4, PFDN4, and CHORDC1. Sci Adv. 2020; 6(18):eaay3051. https://doi.org/10.1126/sciadv.aay3051. PMid:32494663 PMCid:PMC7190312.
134. Brase JC, Johannes M, Schlomm T, *et al*. Circulating miRNAs are correlated with tumor progression in prostate cancer. Int J Cancer. 2011; 128(3):608-616. https://doi.org/10.1002/ijc.25376. PMid:20473869.
135. Mitchell PS, Parkin RK, Kroh EM, *et al*. Circulating microRNAs as stable blood-based markers for cancer detection. Proc Natl Acad Sci USA. 2008; 105(30):10513-10518. https://doi.org/10.1073/pnas.0804549105. PMid:18663219 PMCid:PMC2492472.
136. Richardsen E, Andersen S, Melbø-Jørgensen C, *et al*. MicroRNA 141 is associated to outcome and aggressive tumor characteristics in prostate cancer. Sci Rep. 2019; 9(1):386. https://doi.org/10.1038/s41598-018-36854-7. PMid:30674952 PMCid:PMC6344505.
137. Gao W, Hong Z, Huang H, *et al*. miR-27a in serum acts as biomarker for prostate cancer detection and promotes cell proliferation by targeting Sprouty2. Oncol Lett. 2018; 16(4):5291-5298. https://doi.org/10.3892/ol.2018.9274.
138. Meng Y, Hu X, Li S, *et al*. miR-203 inhibits cell proliferation and ERK pathway in prostate cancer by targeting IRS-1. BMC Cancer. 2020; 20(1):1028. https://doi.org/10.1186/s12885-020-07472-2. PMid:33109107 PMCid:PMC7590475.
139. Saini S, Majid S, Yamamura S, *et al*. Regulatory role of mir-203 in prostate cancer progression and metastasis. Clin Cancer Res. 2011; 17(16):5287-98. https://doi.org/10.1158/1078-0432.CCR-10-2619. PMid:21159887.
140. Viticchiè G, Lena AM, Latina A, *et al*. MiR-203 controls proliferation, migration and invasive potential of prostate cancer cell lines. Cell Cycle. 2011; 10(7):1121-1131. https://doi.org/10.4161/cc.10.7.15180. PMid:21368580.
141. Waseem M, Ahmad MK, Srivatava VK, *et al*. Evaluation of miR-711 as novel biomarker in prostate cancer progression. Asian Pac J Cancer Prev. 2017; 18(8):2185-2191.
142. Kiener M, Chen L, Krebs M, *et al*. miR-221-5p regulates proliferation and migration in human prostate cancer cells and reduces tumor growth in vivo. BMC Cancer. 2019; 19(1):627. Published 2019 Jun 25. https://doi.org/10.1186/s12885-019-5819-6. PMid:31238903 PMCid:PMC6593572.
143. Verma S, Pandey M, Shukla GC, *et al*. Integrated analysis of miRNA landscape and cellular networking pathways in stage-specific prostate cancer. PLoS One. 2019; 14(11):e0224071. https://doi.org/10.1371/journal.pone.0224071. PMid:31756185 PMCid:PMC6874298.
144. Arbyn M, Weiderpass E, Bruni L, *et al*. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health. 2020; 8(2):e191-e203. https://doi.org/10.1016/S2214-109X(19)30482-6.
145. Ferlay J, Colombet M, Soerjomataram I, *et al*. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019; 144(8):1941-1953. https://doi.org/10.1002/ijc.31937. PMid:30350310.
146. Šarenac T, Mikov M. Cervical Cancer, Different Treatments and Importance of Bile Acids as Therapeutic Agents in This Disease [Published 2019 Jun 4]. Front Pharmacol. 2019; 10:484. https://doi.org/10.3389/fphar.2019.00484. PMid:31214018 PMCid:PMC6558109.
147. Roura E, Travier N, Waterboer T, *et al*. The Influence of Hormonal Factors on the Risk of Developing Cervical Cancer and Pre-Cancer: Results from the EPIC Cohort [published correction appears in PLoS One. Jan 25 2016; 11(3):e0151427]. PLoS One. 2016; 11(1):e0147029. https://doi.org/10.1371/journal.pone.0147029. PMid:26808155 PMCid:PMC4726518.
148. Xu J, Zhang W, Lv Q, Zhu D. Overexpression of miR-21 promotes the proliferation and migration of cervical cancer cells via the inhibition of PTEN. Oncol Rep. 2015; 33(6):3108-3116. https://doi.org/10.3892/or.2015.3931. PMid:25963606.
149. Nanthamongkolkul K, Hanprasertpong J. Predictive Factors of Pelvic Lymph Node Metastasis in Early-Stage Cervical Cancer. Oncol Res Treat. 2018; 41(4):194-198. https://doi.org/10.1159/000485840. PMid:29562222.
150. Guo H, Dai Y, Wang A, *et al*. Association between expression of MMP-7 and MMP-9 and pelvic lymph node and para-aortic lymph node metastasis in early cervical cancer. J Obstet Gynaecol Res. 2018; 44(7):1274-1283. https://doi.org/10.1111/jog.13659. PMid:29767419.
151. Wright JD, Huang Y, Ananth CV, *et al*. Influence of treatment center and hospital volume on survival for locally advanced cervical cancer. Gynecol Oncol. 2015; 139(3):506-512. https://doi.org/10.1016/j.ygyno.2015.07.015. PMid:26177552 PMCid:PMC4679418.
152. Liu Z, Hu K, Liu A, *et al*. Patterns of lymph node metastasis in locally advanced cervical cancer. Medicine (Baltimore). 2016; 95(39):e4814. https://doi.org/10.1097/MD.0000000000004814. PMid:27684810 PMCid:PMC5265903.
153. Shen G, Zhou H, Jia Z, Deng H. Diagnostic performance of diffusion-weighted MRI for detection of pelvic metastatic lymph nodes in patients with cervical cancer: A systematic review and meta-analysis. Br J Radiol. 2015;

88(1052):20150063. https://doi.org/10.1259/bjr.20150063. PMCid:PMC4651381.

154. Liu J, Li Y, Chen X, *et al*. Upregulation of miR-205 induces CHN1 expression, which is associated with the aggressive behaviour of cervical cancer cells and correlated with lymph node metastasis. BMC Cancer. 2020; 20(1):1029. https://doi.org/10.1186/s12885-020-07478-w. PMid:33109127 PMCid:PMC7590479.
155. Majid S, Dar AA, Saini S, *et al*. MicroRNA-205-directed transcriptional activation of tumor suppressor genes in prostate cancer. Cancer. 2010; 116(24):5637-5649. https://doi.org/10.1002/cncr.25488. PMid:20737563 PMCid:PMC3940365.
156. Kim JS, Yu SK, Lee MH, *et al*. MicroRNA-205 directly regulates the tumor suppressor, interleukin-24, in human KB oral cancer cells. Mol Cells. 2013; 35(1):17-24. https://doi.org/10.1007/s10059-013-2154-7. PMid:23212344 PMCid:PMC3887855.
157. Sanz-Moreno V, Gadea G, Ahn J, *et al*. Rac activation and inactivation control plasticity of tumor cell movement. Cell. 2008; 135(3):510-523. https://doi.org/10.1016/j.cell.2008.09.043. PMid:18984162.
158. Kozma R, Ahmed S, Best A, Lim L. The GTPase-activating protein n-chimaerin cooperates with Rac1 and Cdc42Hs to induce the formation of lamellipodia and filopodia. Mol Cell Biol. 1996; 16(9):5069-5080. https://doi.org/10.1128/MCB.16.9.5069. PMid:8756665 PMCid:PMC231508.
159. Xie H, Zhao Y, Caramuta S, Larsson C, Lui WO. miR-205 expression promotes cell proliferation and migration of human cervical cancer cells. PLoS One. 2012; 7(10):e46990. https://doi.org/10.1371/journal.pone.0046990. PMid:23056551 PMCid:PMC3463520.
160. Dhar A, Ray A. The CCN family proteins in carcinogenesis. Exp Oncol. 2010 Mar; 32(1):2-9. PMID: 20332765.
161. Wei YQ, Jiao XL, Zhang SY, *et al*. MiR-9-5p could promote angiogenesis and radiosensitivity in cervical cancer by targeting SOCS5. Eur Rev Med Pharmacol Sci. 2019; 23(17):7314-7326.
162. Edatt L, Haritha K, Sruthi TV, Aswini P, Kumar Sameer VB. 2- Deoxy glucose regulate MMP-9 in a SIRT-1 dependent and NFkB independent mechanism. Mol Cell Biochem. 2016; 423: 197-206. https://doi.org/10.1007/s11010-016-2837-4. PMid:27704463.
163. Raji GR, Sruthi TV, Edatt L, *et al*. Horizontal transfer of miR-106a/b from cisplatin resistant hepatocarcinoma cells can alter the sensitivity of cervical cancer cells to cisplatin [Published in Epub. 2017 Jul 11]. Cell Signal. 2017 Oct; 38:146-158. PMID: 28709644. https://doi.org/10.1016/j.cellsig.2017.07.005. PMid:28709644.
164. Xu F, Li Y, Fan L, *et al*. Preoperative SCC-Ag and thrombocytosis as predictive markers for pelvic lymphatic metastasis of squamous cervical cancer in early FIGO stage. J Cancer. 2018; 9(9):1660-1666. https://doi.org/10.7150/jca.24049. PMid:29760805 PMCid:PMC5950596.
165. Zhang L, Zhan X, Yan D, Wang Z. Circulating MicroRNA-21 Is Involved in Lymph Node Metastasis in Cervical Cancer by Targeting RASA1. Int J Gynecol Cancer. 2016; 26(5):810-816. https://doi.org/10.1097/IGC.0000000000000694. PMid:27101583.
166. Wang JY, Chen LJ. The role of miRNAs in the invasion and metastasis of cervical cancer. Biosci Rep. 2019; 39(3):BSR20181377. https://doi.org/10.1042/BSR20181377. PMid:30833362 PMCid:PMC6418402.
167. Zhang Z, Wang J, Wang X, *et al*. MicroRNA-21 promotes proliferation, migration, and invasion of cervical cancer through targeting TIMP3. Arch Gynecol Obstet. 2018; 297(2):433-442. https://doi.org/10.1007/s00404-017-4598-z. PMid:29177591.
168. Tang Y, Zhao Y, Ran J, Wang Y. MicroRNA-21 promotes cell metastasis in cervical cancer through modulating epithelial-mesenchymal transition. Oncol Lett. 2020; 19(4):3289-3295. https://doi.org/10.3892/ol.2020.11438.
169. Trahey M, Wong G, Halenbeck R, *et al*. Molecular cloning of two types of GAP complementary DNA from human placenta. Science. 1988; 242(4886):1697-1700. https://doi.org/10.1126/science.3201259. PMid:3201259
170. Wei WF, Zhou CF, Wu XG, *et al*. MicroRNA-221-3p, a TWIST2 target, promotes cervical cancer metastasis by directly targeting THBS2. Cell Death Dis [Published 2017 Dec 14.]. 2017; 8(12):3220. https://doi.org/10.1038/s41419-017-0077-5. PMid:29242498 PMCid:PMC5870596.
171. Tan Y, Wang H, Zhang C. MicroRNA-381 targets G protein-Coupled receptor 34 (GPR34) to regulate the growth, migration and invasion of human cervical cancer cells [published online ahead of print, 2020 Oct 18]. Environ Toxicol Pharmacol. 2020; 81:103514. https://doi.org/10.1016/j.etap.2020.103514. PMid:33086148.
172. Chen Y, Zhang W, Yan L, Zheng P, Li J. miR-29a-3p directly targets Smad nuclear interacting protein 1 and inhibits the migration and proliferation of cervical cancer HeLa cells. Peer J. 2020; 8:e10148. https://doi.org/10.7717/peerj.10148. PMid:33150075 PMCid:PMC7583608.
173. Wang S, Gao B, Yang H, *et al*. MicroRNA-432 is downregulated in cervical cancer and directly targets FN1 to inhibit cell proliferation and invasion. Oncol Lett. 2019; 18(2):1475-1482. https://doi.org/10.3892/ol.2019.10403.
174. Chen Y, Ma C, Zhang W, Chen Z, Ma L. Down-regulation of miR-143 is related with tumor size, lymph node metastasis and HPV16 infection in cervical squamous cancer. Diagn Pathol. 2014; 9:88. https://doi.org/10.1186/1746-1596-9-88. PMid:24774218 PMCid:PMC4039059.

175. Nambaru L, Meenakumari B, Swaminathan R, Rajkumar T. Prognostic significance of HPV physical status and integration sites in cervical cancer. Asian Pac J Cancer Prev. 2009; 10(3):355-360.
176. Poyyakkara A, Raji GR, Kunhiraman H, *et al*. ER stress mediated regulation of miR23a confer HeLa cells better adaptability to utilize glycolytic pathway. J Cell Biochem. 2018; 4907-4917. https://doi.org/10.1002/jcb.26718 PMid:29377281.
177. Chen S, Gao C, Wu Y, Huang Z. Identification of prognostic miRNA signature and lymph node metastasis-related key genes in cervical cancer. Front Pharmacol. 2020; 11:544. https://doi.org/10.3389/fphar.2020.00544. PMid:32457603 PMCid:PMC7226536.
178. Azizmohammadi S, Safari A, Azizmohammadi S, *et al*. Molecular identification of miR-145 and miR-9 expression level as prognostic biomarkers for early-stage cervical cancer detection. QJM. 2017; 110(1):11-15. https://doi.org/10.1093/qjmed/hcw101. PMid:27345415.
179. Li M, Li BY, Xia H, Jiang LL. Expression of microRNA-142-3p in cervical cancer and its correlation with prognosis. Eur Rev Med Pharmacol Sci. 2017; 21(10):2346-2350.
180. Yadav, S. S., Prasad, S. B., Prasad, C. B., Pandey*et al*. CXCL12 is a key regulator in tumor microenvironment of cervical cancer: an in vitro study. Clin Exp Metastasis. 2016; 33 (5), 431-439. https://doi.org/10.1007/s10585-016-9787-9. PMid:26970955.
181. Serrano, M. L., Romero, A., Cendales, R., *et al*. Serum levels of insulin-like growth factor-I and -II and insulin-like growth factor binding protein 3 in women with squamous intraepithelial lesions and cervical cancer. Rev. Del Instituto Nacional Salud. 2006; 26 (2), 258-268.
182. Kümmel S, Eggemann H, Lüftner D, *et al*. Significant changes in circulating plasma levels of IGF1 and IGFBP3 after conventional or dose-intensified adjuvant treatment of breast cancer patients with one to three positive lymph nodes. Int J Biol Markers. 2007; 22(3):186-193. https://doi.org/10.5301/JBM.2008.1561, https://doi.org/10.1177/172460080702200304. PMid:17922461.
183. Huang, Z., Zhu, D.,Wu, L., *et al*. Six Serum-Based miRNAs as Potential Diagnostic Biomarkers for Gastric Cancer. [Published in Cancer Epidemiol]. Biomarkers Prev. 2017; 26 (2):188-196. https://doi.org/10.1158/1055-9965.EPI-16-0607. PMid:27756776.
184. Zhou, Y., Zhang, Q., Gao, G., *et al*. Role of WDHD1 in human papillomavirus-mediated oncogenesis identified by transcriptional profiling of E7-expressing cells. J Virol. 2016; 90 (13), 6071- 6084. https://doi.org/10.1128/JVI.00513-16. PMid:27099318 PMCid:PMC4907231.
185. Liu, B., Hu, Y., Qin, L., *et al*. MicroRNA-494-dependent WDHDI inhibition suppresses epithelial-mesenchymal transition, tumor growth and metastasis in cholangiocarcinoma. Digestive Liver Dis. 2019; 51(3), 397-411. https://doi.org/10.1016/j.dld.2018.08.021. PMid:30314946.
186. Cheng, Y., Yang, B., Xi, Y., and Chen, X. RAD51B as a potential biomarker for early detection and poor prognostic evaluation contributes to tumorigenesis of gastric cancer. J Int Soc. Oncodevelopmental Biol Med. 2016; 37(11):14969-14978. https://doi.org/10.1007/s13277-016-5340-3. PMid:27651161.
187. Hang, D., Zhou, W., Jia, M., *et al*. Genetic variants within microRNA-binding site of RAD51B are associated with risk of cervical cancer in Chinese women. Cancer Med. 2016; 5(9):2596-2601. https://doi.org/10.1002/cam4.797. PMid:27334422 PMCid:PMC5055154.
188. Yang, L., Shi, T., Liu, F., *et al*. REV3L, a promising target in regulating the chemosensitivity of cervical cancer cells. PloS One. 2015; 10(3):e0120334. https://doi.org/10.1371/journal.pone.0120334. PMid:25781640 PMCid:PMC4364373.
189. Zhu, X., Zou, S., Zhou, J., *et al*. REV3L, the catalytic subunit of DNA polymerase z, is involved in the progression and chemoresistance of esophageal squamous cell carcinoma. Oncol Rep. 2016; 35(3):1664-1670. https://doi.org/10.3892/or.2016.4549 PMid:26752104.