Review Article

The Roles of MicroRNA-133 in Gynecological Tumors

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Abstract

MicroRNAs are noncoding small RNAs that regulate gene expression posttranscriptionally. They act as a key role not only in the body development but also in many human diseases, including malignant tumors. With evidence of the complex role of miR-133 during gynecological malignancies initiation and progression are gradually emerging, miR-133 shows suppressive function by inhibiting tumor proliferation, invasion, and metastasis or acts as an oncogene by promoting tumor initiation, growth and invasion, depending on different tumor types and differentiation. In this review, we summarize the role and related regulatory methods of miR-133 in gynecological cancers. Moreover, then, we analyze and clarify the research status of other microRNAs acting on similar genes and pathways in gynecological tumors and look forward to their future research directions. This review may provide new expectations for applying miR-133 as diagnostic and prognostic biomarkers in gynecological tumors.

Keywords: Biomarker, gynecological tumors, MicroRNA-133, therapy

Introduction

MicroRNAs (miRNAs) are a class of small (18–25 nt) noncoding RNAs encoded by endogenous genes that are involved in the regulation of posttranscriptional gene expression in plants and animals.[1] The production of mature miRNAs requires several key steps. First, long primary transcripts (pri-miRNAs) are transcribed and further cleaved into pre-miRNAs.[2] Then, the pre-miRNAs are further cleaved by RNase III family enzymes (Dicer) into miRNAs.[3,4] MiRNAs bind to the target mRNA with a complementary sequence, playing a regulatory role.[5] Studies have shown that approximately 70% of mammalian miRNAs are located in the transcription units.[6] The miRNAs target sequences are located at the 3' untranslated regions (UTRs),[1] the 5' UTRs[7] and coding regions[8] of related mRNA. Studies showed that more than 30% of protein-coding genes are regulated by miRNAs. The dysregulation and dysfunction of miRNAs are related to human diseases, and aberrant miRNA expression is well recognized as a significant process in the development of cancer.

The miRNA-133 family, primely classified as myomiRNAs, that consists of miR-133a and miR-133b that only a single nucleotide at the 3' end of them is different, is widely studied in human diseases. MiR-133a can be generated by two different genes: MiR-133a-1 and miR-133a-2 that share identical mature sequences. MiR-133a-1, miR-133a-2, and miR-133b are located on human chromosome 18, 20, 6, and transcribed as bicistronic transcripts together with miR-1-2, miR-1-1, and miR-206, respectively. MiR-133 is first identified in the heart and skeletal muscle,[9] and it also plays an important role in the oncogenic and suppressive functions in different kinds of cancers,[10] including ovarian cancer,[11-13] colorectal cancer,[14,15] osteosarcoma,[16,17] and recently gastric cancer[18,19] and so on. MiR-133 recently showed increasing key functions in the initiation and development

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of gynecological cancers. Now, the roles of miR-133 in gynecological cancers will be summarized in this review.

Suppressive Functions in Ovarian Cancer

The vital roles of miR-133 in the pathogenesis of epithelial ovarian cancer (EOC) are reported by many researches [Figure 1]. The present study proves that miR-133a[11,20] and miR-133b[21,22] are both significantly down regulating in ovarian cancer cell lines and tumor tissue samples[11,20,23] compared with normal colon epithelium cells,[24] normal ovarian tissue, and endometriosis.[25] Significantly reduced expression of miR-133a and miR-133b is both correlated with advanced clinical stages, poor histological differentiation, and lymph node metastasis.[11,21,22] Further studies found that the suppressive effects of miR-133a are mediated by targeting 3′-UTR of insulin-like growth factor 1 receptor[13] and miR-133b targets the connective tissue growth factor to regulate epithelial-mesenchymal transition (EMT).[22] The overexpression of miR-133b was shown to inhibit proliferation and invasion of OC cells through decreased the phosphorylation of Erk1/2 and Akt, ultimately suppressing of the MAPK and PI3K/Akt signaling pathways by targeting epidermal growth factor receptor. Furthermore, the overexpression of miR-133a and miR-133b can markedly inhibit the cell viability, proliferation, invasion, and migration by inducing G0/G1-phase cell cycle arrest,[11,13,22,24,26] which reveals the critical role that miR-133 plays in the pathogenesis and development of EOC. Recent studies demonstrated that main sponge molecules, LncRNA HOXD-AS1, and LncRNA PVT1, on the upstream position of miR-133a, playing a competing role in regulating through a direct binding of complementary sequence of miR-133a,[12,26] promoting the proliferation, invasion, and EMT process in EOC cells through activating Wnt/β-catenin signaling pathway.[12] Li *et al*. further demonstrated that miR-145 targets c-myc oncogene which recruiting DNMT3A to the miR-133b promoter inhibiting the expression of miR-133b through suppressing DNMT3A-mediated DNA methylation. MiR-145 can also inhibit the Warburg effect through DNMT3A/miR-133b/PKM2 pathways.[21] SLC6A1 mRNA function as a competing endogenous RNA (ceRNA) that regulates CDX2 expression by competitively binding with miR-133a and the upregulating of miR-133a will lead to a simultaneous decrease of both SLC6A1 and CDX2, which inhibits the proliferation, migration, and invasion of EOC cells.[27] Our team firstly reported that miR-133a can suppress the oncogenic function of glycogen phosphorylase B (PYGB) gene both *in vivo* and *in vitro* through directly bound to 3′-UTR of PYGB and then Wnt/β-catenin pathway is inhabited in OC cell, which significantly suppressing OC cell proliferation, invasion, and migration.[20] Furthermore, Chen *et al*.[28] verified the expression of miR-133b was significantly lower in clinical primary resistant ovarian carcinomas than in the chemotherapy-sensitive carcinomas. Further research in drug-resistant cell lines of ovarian cancer (A2780) revealed that miR-133b may reduce ovarian cancer drug resistance by inhibiting the expression of the drug resistance-related proteins, glutathione S-transferase-π, and multidrug resistance protein 1 which shows that miR-133 may play an important role in drug resistance of ovarian cancer.

Oncogenetic and Tumor-suppressive Roles in Cervical Cancer

The vital roles of miR-133 have been demonstrated adverse functions, both oncogenic and suppressive functions, in the pathophysiology of cervical cancer. Through microarrays analysis of cervical carcinoma, Qin *et al*. found that the level of miR-133b expression was progressively elevated throughout advancing stages in cervical carcinoma tissues. Cellular studies showed that the elevation of miR-133b deregulates the Akt1 and ERK signaling pathways through direct effects on the mammalian sterile 20-like kinase

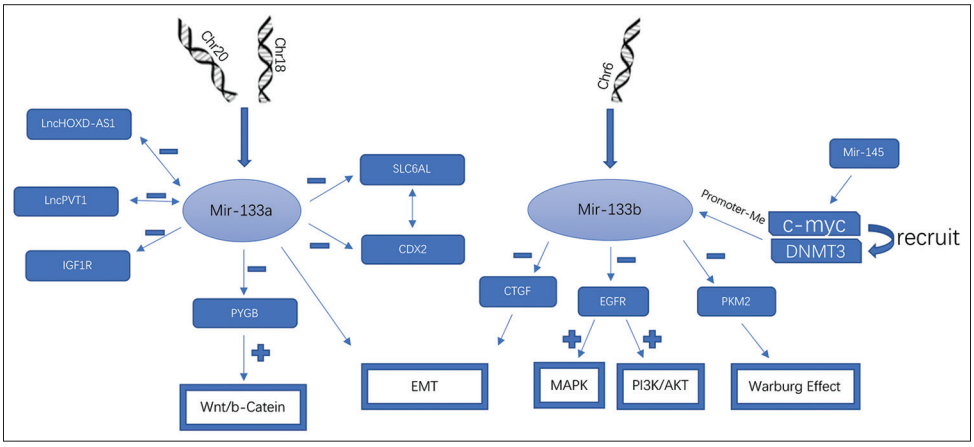

Figure 1: Molecular mechanism of mir-133 in ovarian cancer. The plus sign represents promotion, minus sign represents inhibition

2 (MST2), cell division control protein 42 homolog (CDC42) and as homolog gene family member A (RHOA) genes activities, resulting in enhanced cell proliferation and colony formation *in vitro* and promoting tumorgenesis and metastasis in nude mice model.[29] Qin *et al*. also identified miR-133b was a key prognostic mark through the ceRNA network analysis. They then performed the Kaplan–Meier survival analysis using the TCGA dataset, and the results revealed that the survival ratio was significantly better in the low-expression miR-133b group.[30] However, two recent studies demonstrated that miR-133b played suppressive function and was reversely regulated by upstream oncogenes Lnc02381 and lncMST1P2 with sponging mechanism, inhibiting cell viability, metastasis and migration in cervical cancer cells[31,32] and in subcutaneous tumor model of nude mice.[31] Adversely, some researches verified that miR-133a exhibits opposite suppressor roles in cervical cancer. Yuan *et al*. reported that the expression level of miR-133a was significantly downregulated both in cervical cancer tissues and cervical tumor cell lines,[33] Research showed that LncRNA NEAT1 acted as a sponge molecules negatively modulating miR-133a expression by targeting 5'UTR of miR-133a. SOX4 was able to act as a downstream target of miR-133a and silencing of SOX4 can restrain progression of cervical cancer; therefore, NEAT1/miR-133a/SOX4 axis plays a significant role in the progression of cervical cancer.[33]

Suppressive Functions in Uterine Malignant Tumors

Mir-133b was firstly reported significant down-regulated in mixed epithelial–mesenchymal uterine tumors in 2013,[34] but no further functional research about miR-133b in this tumors is reported. Two years later, Yamamoto *et al*. reported suppressive roles that miR 1/133a cluster plays in endometrial cancer (EC). They found that both miR-1 and miR-133a are downregulated in EC specimens and EC cell lines. Their target gene phosphodiesterase 7A (PDE7A), having one binding site for both miR-1 and miR-133a on the 3'UTR, an enzyme that hydrolyses intracellular cAMP, is reversely upregulated. The overexpression of miR-1/133a leaded to a decreased expression level of PDE7A and ultimately inhibited EC cell migration and invasion.[35] Recently, Shi *et al*. unveiled a whole new discovery that miR-133a, which regulates the expression of FOXL2, was present in exosomes derived from the culturing supernatants of Ishikawa and HEC-1-A EC cells and that could be delivered to normal endometrial cells.[36] This study might play an important role in the progression as well as diagnosis of EC. In addition, an animal model of hamster uterus experiment done by Padmanabhan *et al*. demonstrated a fact that downregulated miR-133a is strongly associated with the promotion stages of neonatal diethylstilbestrol-induced neoplasia (endometrial adenocarcinoma). These results have further indicated the key role of miR-133 in the embryonal development stage.[37]

Similar Function Micro-rnas in Ovarian Cancer

As illuminated above, miR-133 is mainly acted on WNT, MAPK, and AKT pathways. Here, we summarize other reported microRNAs impacted on the same pathway in ovarian cancer to predict the potential further functions that may be effected on ovarian cancer [Figure 2 and Table 1]. The overexpression of miR-16 and miR377 can regulate metastatic capability by inhibiting the process of EMT and inactivating the Wnt/β-catenin pathway[38,39] and restoration of miR-338 will attenuate MACC1 and Met overexpression-induced EMT and activities of Wnt/β-catenin and MEK/ERK signaling *in vitro* and *in vivo*.[40] Adversely restraining the expression of miR-27a that regulating FOXO1 can inhabit cell migration and invasion by inhibiting EMT and inactivating of the Wnt/β-catenin pathway in ovarian cells.[41] These evidences indicate that the microRNAs-induced activation of the Wnt/β-catenin pathway often promotes the EMT process in OC. Chen *et al*. found that miR-92a-1 is regulated by STAT3 and targets DKK1 the canonical Wnt pathway antagonist, to inhibit the Wnt pathway. The STAT3-miRNA-92-Wnt signaling pathway regulates cancer stem cell-like characteristics and is related to chemoresistance in ovarian cancer cells.[42] Majem *et al*. unveiled miR-654 differentially expressed between short term (overall survival of <3 years) and long term (overall survival of more than 8 years) survival groups. Kaplan–

Table 1: Similar microRNAs roles in ovarian cancer

miRNAs	Targets	Pathways	Function	Reference
MiR-16 and MiR-377	CUL4A	Wnt/β-catenin	Suppresses EMT process	[36,37]
MiR-338	MACC1	Wnt/β-catenin and MEK/ERK	Suppresses met-induced EMT process	[38]
MiR-27a	FOXO1	Wnt/β-catenin	Suppresses EMT process	[39]
MiR-92a-1	DKK1	Wnt/β-catenin	Modulates CSC-like characteristics and chemoresistance	[40]
MiR-654-5p	CDCP1 and PLAGL2	MYC and Akt and Wnt	Reduces tumor cell viability	[41]

EMT: Epithelial-mesenchymal transition, CSC: Cancer stem cell, ERK: Extracellular regulated kinases,MEK(MAPKK):Mitogen-activated protein kinase kinase, MYC:V-Myc myelocytomatosis viral oncogene homolog

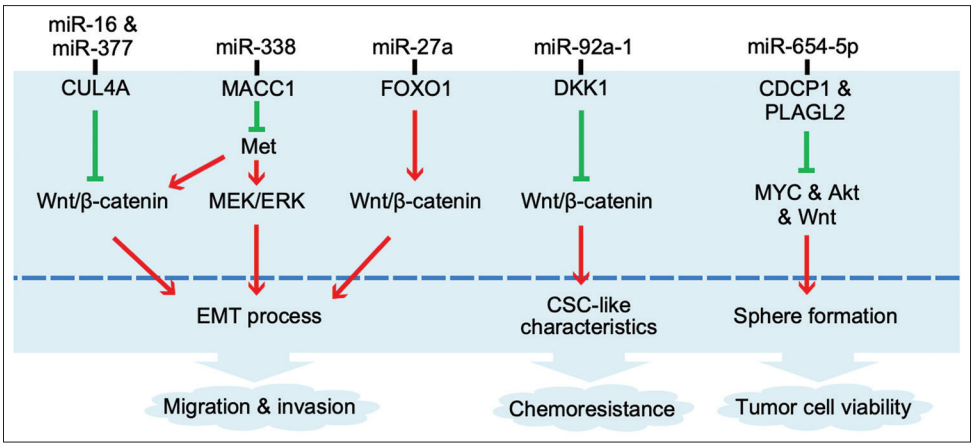

Figure 2: Similar function miRNAs in ovarian cancer. Black indicators represent binding, red indicators represent promotion, and green indicators represent inhibition

Meier survival curves from HGSC tumors reflected that high miR-654 expression related to poorer survival, suggesting a prognostic role for miR-654 levels in OC. In addition, the results demonstrate that miR-654 promoter region is hypermethylated in both OC cell lines and tissues, which can be responsible in part for the low miR-654 levels and suggests that epigenetic silencing could be one of the possible mechanisms of microRNAs regulation. The overexpression of miR-654 reduces viability in normal OC cell lines and OC patient-derived ascitic cells, sensitizing OC cells to paclitaxel and impairing tumor growth *in vivo*. Further investigation verified that miR-654 mainly targets CDCP1 and PLAGL2 genes which in turn modulate the MYC, AKT, and Wnt pathways in OC.[43]

Conclusion

Increasing evidence shows that miR-133 plays a vital role in the initiation and progression of human malignancies. On the one hand, miR-133 mainly inhibits cell proliferation, invasion, metastasis, and regulates EMT in ovarian cancer and uterine malignant tumors. On the other hand, miR-133 shows the opposite effect in cervical cancer. However, more in-depth researches of miR-133 in fields of gynecological cancers, such as drug sensitivity, epigenetics alterations, prediction role of clinical prognosis, and other clinical implications, have not been reported, and further related researches are expected to provide sufficient evidences to explain the functions of miR-133.

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Conflicts of interest

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