Cancer in Females

REVIEW ARTICLE

The relationship between microRNAs and EMT process in cervical cancer

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ABSTRACT

There is still a high prevalence of cervical cancer (CC) in females. The treatment effect of advanced-stage CC patients is poor and once the tumour transfer to other body organs, the final survival rate decreases dramatically. The epithelial-mesenchymal transition (EMT) process is a critical factor in the progression and metastasis of CC. EMT allows epithelial cells to acquire mesenchymal characteristics, and enables them to invade surrounding tissues and migrate to distant sites. This transition enhances the aggressiveness and metastatic potential of CC cells, and contributes significantly to disease advancement and spread. Understanding and targeting the mechanisms regulating EMT are crucial for developing effective therapeutic interventions to prevent or inhibit the metastasis of CC. This process was firstly recognized as a special cell differentiation process during organogenesis, in more recent years it has been re-known as a significant component in the progression and metastasis. Multiple microRNAs (miRNAs) have been shown to act as controllers of different EMT transcription factors like twist, snail, and ZEB1/2 proteins. All these special miRNAs were discussed in detail in this review. In addition, long noncoding RNAs (lncRNAs) and circRNAs can regulate the miRNA/EMT axis as upstream mediators, and some anti-tumor agents can target the miRNA/EMT axis to affect the metastasis of CC. In summary, this study highlighted a broad range of miRNAs that may play critical roles in the EMT process of CC. Understanding the relationship between miRNAs and EMT could provide valuable insights into developing new and more effective therapeutic strategies to combat CC progression and metastasis. By targeting these miRNAs and their associated pathways involved in the EMT process, it may be possible to develop more targeted and personalized treatments to ameliorate the negative effects of cervical pathogenesis through EMT.

Key words: cervical cancer, epithelial to mesenchymal transition, microRNA, cancer therapy

INTRODUCTION

Cervical cancer (CC) remains as a common gynecological malignancy worldwide, with significantly higher incidence and mortality rates in low- and middle-income countries and currently affects approximately one million global women. Based on a global systematic literature review, 37.0% of all CCs are diagnosed at the locally advanced stage.[1] The majority of CC cases are related to persistent the human papillomavirus (HPV) infection; however, HPV alone is not sufficient. Other molecular components, including the epithelial-mesenchymal transition (EMT) process, are also associated with the development of CC.

EMT is a biological phenomenon where epithelial cells undergo a loss of cell-cell adhesion and gain mesenchymal traits.[2] The process is characterized by a reduction in epithelial markers like E-cadherin, cytokeratin, and β-catenin, and an elevation in

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mesenchymal markers such as N-cadherin, vimentin, and fibronectin.[3] The hallmark of EMT is the degradation of the basement membrane and appearance of mesenchymal cells that can migrate from their epithelial origin.[4] Initially described as a fundamental feature of embryonic development, EMT has been discovered to be essential in processes such as neural crest migration,[5] palate fusion,[6] and heart valve formation.[7]

Numerous studies indicate that the EMT process correlates with advanced CC in patients. Despite striking improvements have been made in surgery combined with radiotherapy, subjects with advanced-stage disease still have a poor prognosis and suffer from poor therapeutic outcomes.[8] Currently, there is a lack of concrete findings that could help halt the progress of CC.

MicroRNAs (miRNAs) have the ability to interact with the 3'untranslated region (UTR) of messenger RNA (mRNA), thereby regulating the expression of mRNA.[9] Based on their specific regulatory roles, MiRNAs can be classified into oncogenic miRNAs and tumor-suppressive miRNAs, both of which are important in diverse biological activities. So far, over 2300 miRNAs have been identified and documented, and researchers are continuously exploring and identifying unknown miRNAs.[10] miRNAs have a role in epigenetically silencing or activating genes, including tumor suppressor genes along with oncogenes, and their regulation brings up new avenues for the design of novel cancer therapeutics.[11]

Research has shown that the metastasis of CC is associated with some classical signaling pathways, the interactions between the molecules of which have been widely studied. Some studies have demonstrated that miRNAs can regulate metastasis by modulating EMT transcription factors and certain signaling cascades. This article provides a review of the interaction between miRNAs and the EMT process in CC, aiming to elucidate the mechanisms by which miRNAs regulate the EMT process of CC cells and to identify potential targets for the treatment of advanced CC cells.

EMT

During the EMT process, epithelial cells undergo a loss of apico-basal polarity and cell-cell adhesion as they acquire mesenchymal characteristics. The EMT process can facilitate the invasion of cancer cells into adjacent tissues and their subsequent metastasis to distant sites. Additionally, the concurrent downregulation of the adhesion protein E-cadherin during the EMT process facilitates the acquisition of migratory capabilities in cancer cells, thereby contributing to the progression of carcinoma.[12] In a typical EMT process, there is a transition in the usage of intermediate filaments from cytokeratins to vimentin. Additionally, there are significant rearrangements in cortical actin filaments in epithelial cells during the EMT. EMT biomarkers encompass a range of proteins, including E-cadherin, N-cadherin, β-catenin and vimentin, which indicate the transition from an epithelial to a mesenchymal phenotype. The loss of E-cadherin expression plays a crucial role in tumor initiation, progression, invasion, and metastatic dissemination, emphasizing the significance of the EMT process.[13,14] E-cadherin functional loss may be caused by germline or somatic mutation of the gene, promoter hypermethylation, and transcriptional suppression.[15] Transcription factors such as Snail1/2, ZEB1/2, and TWIST1/2 can initiate the EMT process by binding to the E-box region of the E-cadherin promoter, resulting in the suppression of E-cadherin expression (Figure 1).[16] CC with an EMT phenotype displays augmented tumour cell motility, invasion along with metastasis in epithelial integrity.

Chronic infection with HPV, particularly strains 16 and 18, is the primary cause of CC. This persistent viral infection can lead to the development of cancerous changes in the cervix.[17] The presence of HPV16 E6 induces the expression of genes typically associated with mesenchymal lineages in epithelial cells. On the other hand, cells that express HPV16 E7 show decreased amounts of E-cadherin and higher amounts of fibronectin and vimentin. These changes suggest a potential role of HPV in promoting characteristics associated with mesenchymal cells, particularly in CC.[18] In simian virus 4 (SV40)-immortalized human keratinocytes, the expression of HPV18 E6 has been associated with the acquisition of a fibroblastoid morphology. This suggests that HPV18 E6 may contribute to the observed mesenchymal-like characteristics in these cells.[19] Overall, based on these data, it can be inferred that there is a correlation between EMT in epithelial malignancies and the presence of aggressive tumors in individuals diagnosed with CC. According to recent research, the majority of cervical malignancies (52%) are E-cadherin positive, with the antigen completely absent in only 10% of tumors.[20] In patients with advanced cervical squamous cell carcinoma who are HPV-positive, there is a decrease in E-cadherin expression and an increase in N-cadherin expression.[21] These results indicate that E-cadherin could be utilized as a standalone prognostic indicator for CC.[22]

Researchers have discovered a further important role of the EMT process. EMT causes differentiated cells to return to a stem cell-like form. The molecular profile of cancer EMT stem cells has been documented to be comparable to that of cancer stem cells (CSCs).[23–26] This

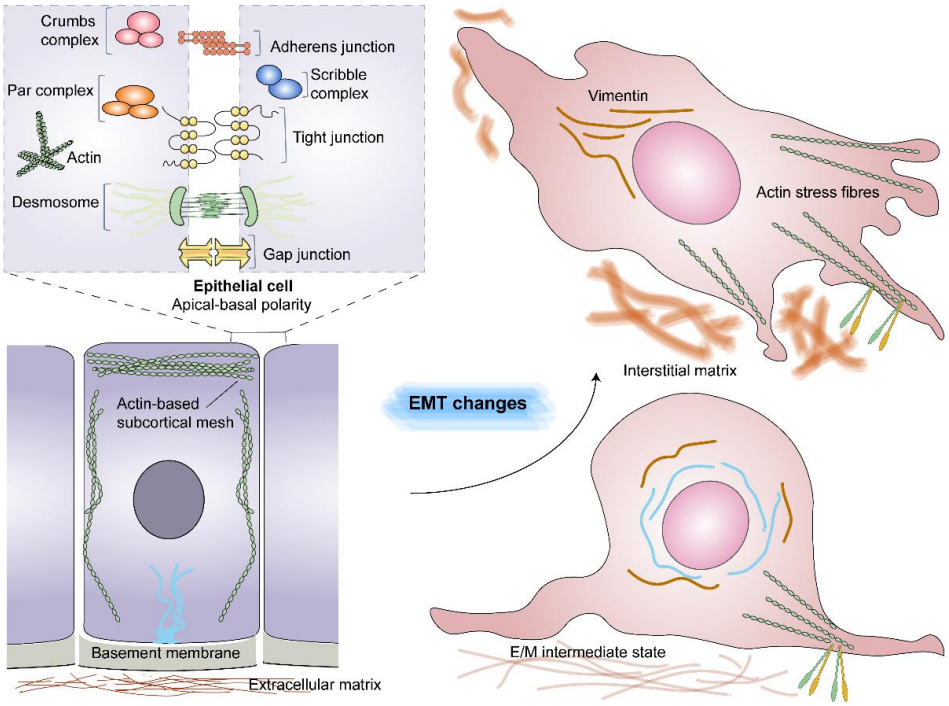

Figure 1. During the epithelial-mesenchymal transition (EMT), epithelial cells undergo molecular changes, including remodeling of the cytoskeleton, loss of apical-basal cell polarity, and weakening of cell-cell adhesion, enabling tumor cells to acquire cell motility and invade the basement membrane.

discovery transformed the idea of CSC biology and offers a new approach for targeting CSCs that focuses on the EMT process.[27] CC cells derived from spheroids exhibit EMT features and CSC traits, and display high expression levels of the CSC biomarker the aldehyde dehydrogenase 1 (ALDH1).[28] These findings imply that targeting the EMT mechanism in CC might result in novel treatment options.

MICRORNAS (MIRNAS)

The human genome contains numerous miRNAs, which have the ability to affect the production of thousands of mRNAs, and play a significant role in regulating protein synthesis within cells.[29] Many miRNAs have significant tissue selectivity and target gene variety across tissues.[30] miRNAs exert significant influence on diverse biological processes encompassing cell proliferation, apoptosis, migration, invasion, angiogenesis, and carcinogenesis. Abnormal and disrupted miRNAs in CC are crucial in initiating and advancing the disease.[31,32] miRNAs Have emerged as epigenetic regulators to affect pathogenesis in many diseases.[33] Furthermore, miRNAs have been found to modulate gynaecological cancer angiogenesis by affecting pro-angiogenic factors and signaling cascades associated with EMT progression.[34] While many miRNAs have been identified as regulators of the EMT process in CC, their specific roles and mechanisms are still not well understood. Some miRNAs function as oncogenes that could promote EMT, while others act as tumor suppressors and inhibit the process. Further research is needed to comprehensively unravel the intricate relationship between miRNAs and the EMT process in CC. Various transcription factors and signaling cascades have been proven to be related to this process. In addition, many methods are used to detect miRNAs, including nanotechnology-based approaches, northern blotting, quantitative reverse transcriptase PCR (qRT-PCR) assessment, microarray technology, as well as molecular biology tools, including miRNA biosensors.[35] These methods make it more convenient for researchers in exploring the association between miRNAs and the EMT process. Exosomal miRNAs have garnered increasing attention in recent years and have been shown to play crucial roles in the pathogenesis of various diseases, including neuroblastoma,[36] prostate cancer,[37] non-small-cell lung cancer,[38] and sepsis.[39] Exosomal miRNAs have been documented to be useful as theranostic biomarkers in treating CC, and could also be related to the EMT process in CC.[40]

MIRNAS CAN TARGET EMT TRANSCRIPTION FACTORS

Emerging reports suggest that EMT transcription factors including Twist Snail and Zeb can direct modulate the EMT process.[41–44] These two EMT transcription factors could affect each other then act together to activate EMT. miRNAs possess the capacity

to suppress the EMT process by modulating the transcription factors associated with EMT either directly or indirectly. (Figure 2).

MiRNAs regulate twist

Twist, consisting of Twist1 and Twist2, belongs to the basic helix-loop-helix (bHLH) family.[45] In recent investigations, researchers have discovered proteins of the Twist family as essential regulators of EMT during embryogenesis and carcinogenesis. Immunohistochemical analysis of CC samples has demonstrated elevated expression levels of Twist. These increased expression levels of Twist have been found to be correlated with poor tumor differentiation and lymph node metastasis.[46] In Caski CC cells, high expression of the Twist gene is observed and inhibiting its expression suppresses cell proliferation and induces apoptosis.[47] The overexpression of Twist in CC is linked to unfavorable clinical outcomes.[48] Moreover, studies have shown that suppressing the Twist gene can enhance the sensitivity of CC cells to paclitaxel chemotherapy.[49] Therefore, this discovery of a potential therapeutic approach for CC holds promise for improved outcomes, offering a promising strategy for treatment. It may also pave the way for the development of more effective therapies in the future.

Multiple research studies have shown how microRNAs regulate Twist and influence the EMT process. miR-214–3p has been shown to inhibit EMT transition and metastasis in endometrial cancer by targeting Twist1.[50] Similarly, miR-186 can reduce Twist1 expression and suppress the EMT process in ovarian cancer cell lines.[51] Furthermore, in CC, microRNA-33a targets Twist1 to suppress EMT and function as a tumor suppressor gene.[52] However, some miRNAs can act as oncogenes, such as microRNA-221–3p, which is targeted by TWIST2. miR-221–3p is highly expressed in CC tissues, especially those with lymphatic metastasis, promoting the EMT process. Additionally, both miR-221–3p and TWIST2 levels are increased in these tissues.[53]

MiRNAs regulate snail

Through immunohistochemical analysis of CC tissues and adjacent tissues, it was found that the expression of Snail was elevated in CC.[54] Further experimental studies revealed that HPV18 could enhance the expression of Snail, thereby leading to enhanced EMT and promoting metastasis of CC.[55] Slug, also known as Snail2, has been observed to exhibit nonlinear dynamic changes. Its upregulation in the initial stages of EMT may promote the transformation of mesenchymal cells, thereby inducing the formation of new tumor blood vessels.[56] These dynamics are potentially specific to CC. Therefore, collectively, findings from these studies suggest that researchs on snail including snail1 and slug hold great importance for the management of CC.

MicroRNAs can regulate the expression of Snail in different types of cancers, with both positive and negative regulation. In non-small cell lung cancer, miR-30a targets Snai1, resulting in the suppression of invasion and metastasis.[57] The activation of p53 induces miR-34a/b/c, which down-regulates Snail.[58] Similarly, in ovarian cancer, miR-137 and miR-34a directly target Snail, resulting in the inhibition of EMT.[59] On the other hand, in glioblastoma, miR-203 targets Snail2 and promotes EMT.[60] microRNAs can target both Snail and Snail2 to affect the EMT process. The relationship between microRNAs and Snail, as confirmed by a series of studies, can help us identify novel targeted therapies for CC.

MiRNAs regulate Zeb

The zinc-finger E-box-binding (ZEB) family, consisting of Zeb1 and Zeb2, plays a vital role as nuclear transcription factors in EMT.[61] The elevated expression of ZEB1 plays a crucial role in promoting the metastasis and progression of diverse cancers, including CC.[62] Clinical evidence has demonstrated a positive relationship between hypoxia-induced Zeb1 and the distribution of tumor-associated macrophages (TAM) in CC progression.[63] Furthermore, the levels of Zeb1 nuclear protein expression play a role in the advancement and spread to lymph nodes of CC *via* the EMT pathway.[64] The results suggest that focusing on Zeb1 could be an advantageous approach for addressing CC.

The effect of microRNAs on the Zeb gene could be bidirectional. In cancerous situations, many microRNAs inhibit Zeb1 expression, blocking EMT.[65] Previous studies identified that miR-484,[62] miR-205,[66] miR-429,[67] miR-139–5p,[68] and miR-525–5p[69] were negatively correlated with serum Zeb1 and can inhibit EMT in CC. Loss or repression of microRNAs targeting Zeb1 in cancer can lead to the upregulation of Zeb1, thereby promoting the process of EMT.[41]

MIRNAS CAN REGULATE EMT-RELATED SIGNALLING PATHWAYS IN CERVICAL CANCER

MiRNAs can inhibit EMT in cervical cancer cells

In the preceding section, we emphasized the ability of microRNAs to target EMT transcription factors. In the next two sections, we would introduce the pathways involved in regulating miRNAs in the EMT process (Figure 3). In this section, we will discuss the role of onco-suppressor microRNAs in inhibiting the EMT

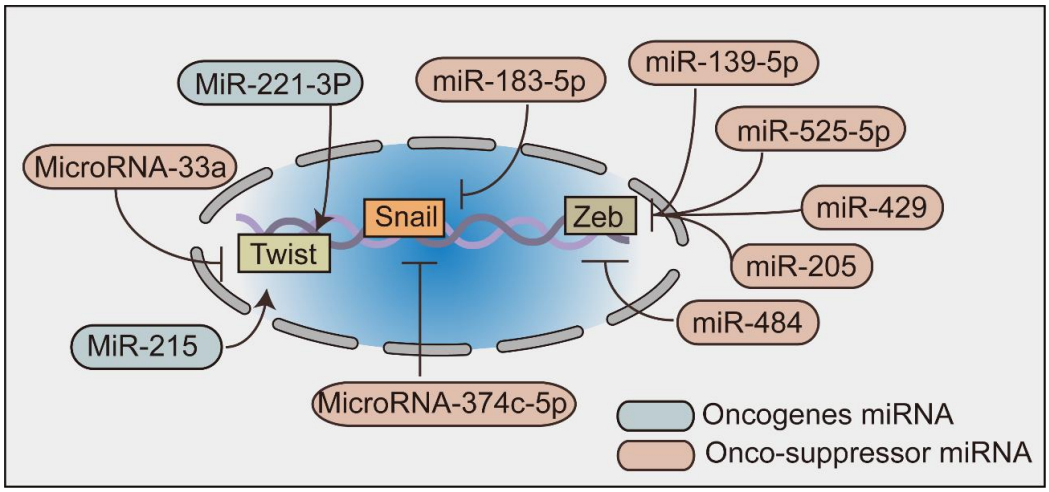

Figure 2. MiRNAs can directly bind transcription factors to affect the EMT process. In this figure, yellow indicates onco-suppressor miRNAs, and grey indicates oncogene miRNAs.

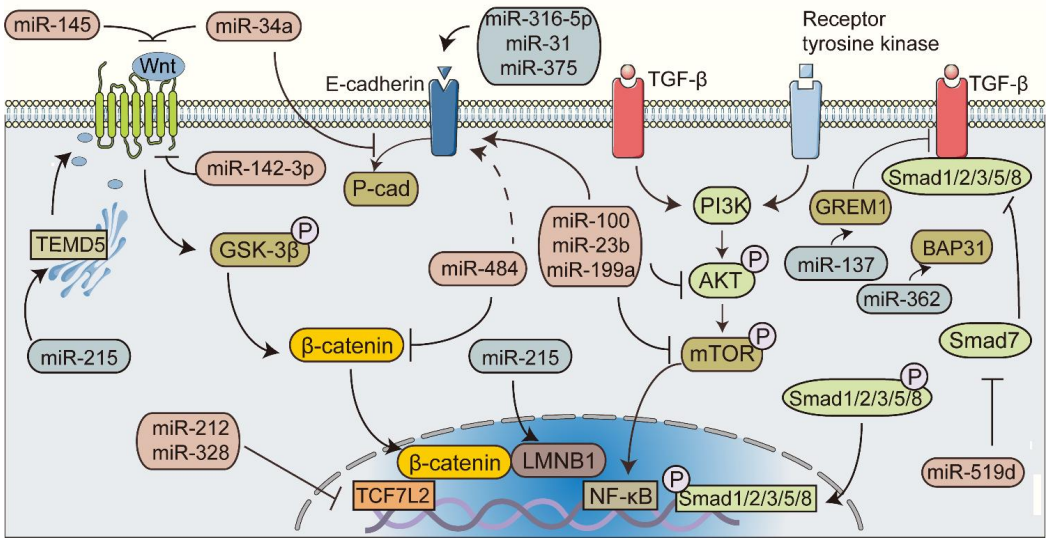

Figure 3. Different miRNAs can affect signaling pathways by targeting different molecules, resulting in a reduction or induction of the EMT process.

process in CC cells. Expression of these microRNAs in tumor tissues is decreased, compared to normal tissues. This decrease in onco-suppressor microRNAs is associated with an unfavorable prognosis for patients.

MiRNAs and the AKT/mTOR/EMT axis

MicroRNAs have been found to regulate the AKT/Mtor pathway,[70–74] which significantly contributes to tumor development and tumorigenesis.[75–77] MicroRNA-23b can act as tumor suppressor by modulating the AKT/mTOR signaling pathway in CC and its inhibition could lead to changes in EMT-related markers and promotes mesenchymal transition in CC.[78] Six1 has been identified as a direct target of MicroRNA-23b. MicroRNA-100[79] and MicroRNA-199a[80] have also been found to regulate the Akt/Mtor/EMT Axis.

MiRNAs and the Wnt/EMT axis

The upregulation of positive modulators of the Wnt/β-catenin signaling pathway, has been shown to increase the activity of genes associated with EMT.[81] Among these, WNT1 is an activator. Li *et al.*[82] found WNT1 and miR-34a exhibit an inverse correlation in primary cervical squamous cell carcinoma tissues. They further demonstrated that miR-34a can regulate the transition from E-cadherin to P-cadherin by inactivating the WNT1/β-catenin pathway. This regulatory mechanism leads to the inhibition of cell proliferation and tumor formation, as demonstrated in both *in vitro* and *in vivo* experiments. Upregulation of miR-142–3p has been shown to downregulate the Frizzled-7 receptor and inhibit EMT in HeLa and SiHa cells through the Wnt signaling pathway.[83] MiR-212 and miR-328 were

discovered to block CC cell EMT by targeting Transcription factor 7 like 2 (TCF7L2), a key element of the Wnt signaling pathway.[84–86] Additionally, Li *et al.*[87] confirmed that upregulation of miR-145 targets WNT2B expression, leading to repression of the Wnt signaling pathway in CC cells.

MiRNAs and the TGFβ/EMT axis

The involvement of the transforming growth factor β (TGFβ) in the development of tumors is multifaceted that initially serves as a tumor suppressor and transforms into an oncogene in later. Additionally, TGFβ plays a crucial role in initiating EMT. EMT activation and the TGF-β/smad pathway were detected in CC tissues and cells, accompanied by decreased miR-137 expression. MiR-137 functions as a suppressor of tumors in CC cells by blocking invasion, movement, and EMT through its interaction with Gremlin 1 (GREM1) and inhibition of the TGF-β/smad pathway.[88] In a separate study, MiR-362 was found to inhibit the TGFβ/Smad pathway, resulting in increased apoptosis and decreased proliferation in CC cells.[89] These findings indicate that the TGFβ/Smad pathway has varying effects on CC at different stages of tumor development and progression.

MiRNAs and the YAP/EMT axis

By targeting Yes-associated protein 1 (YAP1), the excessive expression of miR-195–5p can impede the EMT progression in CC cells.[90] The potential of the miR-195–5p/YAP1/EMT axis as a molecular target for targeted therapy in CC is evident.

Other miRNAs

In addition, clinical studies have shown that many other miRNAs have been associated with the EMT process in CC. Table 1 lists the miRNAs that can inhibit the EMT process in CC cells.

MiRNAs can induce the EMT in cervical cancer cells

MiRNAs and the Wnt/EMT axis

In this part we will introduce the way how microRNA induce EMT process in CC cells. The Wnt signaling pathway is widely known to be crucial in various cancers, including CC, and represents a conservative EMT-related signaling pathway. He abnormal activation of the Wnt signaling pathway leads to deregulated growth and cancer. Zhen *et al.*[107] identified a novel microRNA in CC cells, named MIR-G-1, which directly targets and upregulates lamin B1 (LMNB1) and TMED5. The increasing expression of TMED5 promotes the EMT process, and the interaction between TMED5 and WNT7B activates the Wnt signaling pathway. Wu *et al.*[108] has verified that miR-361–5p is inversely correlated with E-cadherin and facilitates CC procession, the process of which dependent on Wnt signaling pathway. MiR-31 and miR-375 can target on E-cadherin and downregulate its expression to induce EMT process in CC.

MiRNAs and the TGF-β/EMT axis

As mentioned above, TGFβ is a main initiator of EMT, and the activation of the TGF-β/smad pathway has been detected in CC. Additionally, studies have shown that TGF-β can induce EMT in an advanced cervical tumor model through 3D printing.[109] MiR-519 d promotes CC metastasis through TGF-β/Smads signaling pathway by downregulating Smad7.[110] miR-375 has been found to depend on cluster of differentiation 36 (CD36) in breast cancer cells and CD36 has been demonstrated to interact with TGF-β and promote the EMT process in CC.[111] However, the relationship between CD36 and miRNA has not been explored in CC and further investigation will be required.

Other miRNAs

In CC, the upregulation of miR-20a targeting F-box and leucine-rich repeat protein 5 (FBXL5) and B cell transposition gene 3 (BTG3) induces the EMT process[112] and is correlated with lymph node metastasis (LNM), histological grade, and tumor diameter in clinical studies.[113] microRNA-21 acts as an oncogene in CC by inducing the upregulation of Vimentin and N-cadherin, downregulation of E-cadherin at the protein level to modulate EMT in HeLa and SiHa cells.[114] MiR-150–5p promotes proliferation and EMT in cervical carcinoma cells by targeting Src kinase signaling inhibitor 1 (SRCIN1).[115] MiR-27b induces the EMT process in CC cells by regulating the expression of E-cadherin, vimentin, and N-cadherin through its direct target, cadherin-11 (CDH11).[116] Moreover, Jin *et al.* found that miR-106b overexpression and disabled-2 (DAB2) knockdown induced EMT in CC cells.[117] To effectively inhibit metastasis of CC cells, it is important to identify and target the signaling pathways that induce EMT. Table 2 presents a list of miRNAs that have been shown to induce EMT in CC cells. Table 2. MicroRNAs induce EMT in CC cells.

MIRNAS ARE RELATED TO THE CHEMORESISTANCE AND CHEMOSENSITIVITY OF CERVICAL CANCER CELLS BY REGULATING THE EMT PROCESS

Although the precise mechanism by which CC cells acquire chemoresistance is unclear, the EMT and miRNAs have been proposed to play important roles in these progresses in several studies.

The association of miR-375 with chemotherapy resistance in CC cells has been validated through both *in vivo* and *in vitro* experiments.[118] Subsequent investig-

Table 1: MiRNAs that inhibit the epithelial-mesenchymal transition (EMT) in cervical cancer cells

MiRNA	Target	Cell line	Change in expression level	References
miRNA-504	PAICS	C33A and HeLa	Down	[91]
miR-377–3p	SGK3	HeLa	Down	[92]
miR-31–3p	Sema4C	CaSki	Down	[93]
miR-526b	PBX3	CaSki and C33A	Down	[94]
miRNA-218	SFMBT1 DCUN1D1	SiHa and HeLa	Down	[95]
miRNA-145	SIP1	C33A and SiHa	Down	[96]
miRNA-200b	RhoE	HeLa	Down	[97]
miRNA-4264	Kaiso (ZBTB33)	HeLa and CaSki	Down	[98]
miRNA-361	HSP90	HeLa and SiHa	Down	[99]
miRNA-124	AEG-1	HeLa and SiHa	Down	[100]
miRNA-506	FOXQ1	CaSki and SiHa	Down	[101]
miRNA-211	MUC4	HeLa and SiHa	Down	[102]
miRNA-504	PAICS	C33A and HeLa	Down	[91]
miR-204–5p	TFAP2A	CaSki and SiHa	Down	[103]
miRNA-374c-5p	Foxc1	SiHa and HeLa	Down	[104]
miRNA-1297	AEG-1	C33A and CaSki	Down	[105]
miRNA-873	GLI1	HeLa and SiHa	Down	[106]

Table 2: MiRNAs that induce the epithelial-mesenchymal transition (EMT) in cervical cancer cells

MiRNA	Target	Cell line	Change of expression level	reference
miRNA-221–3P	TWIST2	SiHa and HeLa	Up	[15]
miRNA-21	unclear	HeLa and SiHa	Up	[16]
miR-125a-3p	FUT6	HeLa	Up	[17]
miR-205	ASPP2	HeLa and SiHa	Up	[18]
miR-141–3p	FOXA2	HeLa and SiHa	Up	[19]
miR-720	RAB35	HeLa	Up	[20]
miR-G-10	TIMP3	HeLa and C33A	Up	[21]

ations have revealed that its mechanism of mediating drug resistance primarily involves the inhibition of E-cadherin expression, thereby fostering the EMT process.[119] In a study conducted by Song *et al.*[120] it was further discovered that miR-375 correlates with radiotherapy resistance in HPV-associated CC, predominantly by impeding the degradation of p53. Future research that focus on the potential correlation between miR-375-induced radiotherapy resistance and the process of EMT in CC will be needed and shed light on the underlying mechanisms and provide valuable insights into the interplay between miRNA regulation, radiotherapy resistance, and EMT in CC cells.

In numerous cancer types, miR-21 has been implicated in chemotherapy resistance. In the case of CC, microRNA-21 demonstrates elevated expression levels and exerts its influence on EMT regulation by directly targeting Smad7 and consequently promotes chemotherapy resistance in advanced stages of CC.[121]

Besides causing chemoresistance, miRNAs have also been found to increase chemosensitivity in CC cells by modulating EMT. MiR-155 has been found to negatively regulate the epidermal growth factor (EGF)-induced EMT and increase the chemosensitivity to Cisplatin (DDP) in human Caski CC cells.[122] Multiple research studies have provided evidence that the reversal of the EMT phenotype can sensitize cisplatin-resistant CC cells. Notably, the targeting of Semaphorin 4C (Sema4C) by miR-25–3p[123] and Quaking (QKI) by miR-574–5p[124] can both impact the EMT process and enhance chemotherapy sensitivity. Based on these findings, it is hypothesized that the exogenous introduction of miRNA mimics could potentially reverse EMT and achieve chemotherapy sensitization in CC.

REGULATION OF MIRNA/EMT IN CERVICAL CANCER CELLS

lncRNAs as main regulators

As previously discussed, miRNAs play a crucial role in regulating the EMT process in CC cells through various molecular pathways. In CC, lncRNAs act as regulators of miRNAs and effectively modulate the expression of key miRNA targets. Notably, lncRNAs can function as competitive endogenous RNAs (ceRNAs) that inhibit

the targets of miRNAs.[125] It is important to note that lncRNAs can exhibit both tumor suppressor gene and oncogene properties in CC.[126]

Acting as tumor suppressor genes, lncRNAs play a crucial role in inhibiting the EMT process in CC cells by targeting various microRNAs. For example, PVT1 is known to directly interact with the miR-195 promoter.[127] LINC00861 functions by up-regulating the expression of phosphatase and tensin homolog (PTEN) through sponging miR-513b-5p.[128] Similarly, lncRNA PTENP1 promotes PTEN expression and induces apoptosis in CC cells through competitive binding with miR-106b.[129] Additionally, overexpression of lncRNA PTCSC3 leads to interactions with the sponge matrix miR-574–5p.[130]

As oncogenes, lncRNAs can promote the EMT process in CC by regulating miRNAs. For example, the LncRNA SPRY4-IT1 regulates the miR-101–3p/ZEB1 axis.[131] LncRNA UCA1 promotes the occurrence of EMT in CC cells by targeting miR-155.[132] LncRNA NEAT1 directly inhibits the expression of miR-361, thereby promoting EMT.[99] Furthermore, lncRNAs can function as competitive ceRNAs and exert their role through miRNA sponge activity. LncRNA-CTS acts as a competitive endogenous RNA for miR-505.[133] LncRNA DANCR acts as a sponge for miR-335–5p, and a miR-335–5p mimic can reverse the upregulation of DANCR and its impact on EMT in CC cells.[134] LncRNA-CTS enhances TGF-β1-induced EMT through miR-505 sponge activity in both *in vitro* and *in vivo* settings.[133] LncRNA LOC105374902 may serve as a ceRNA for miR-1285–3p, promoting the expression of ribosomal protein L14 (RPL14) and facilitating EMT in CC cells.[135] LncRNA TDRG1 promotes the EMT process in CC cells by sponge binding to miR-214–5p and targeting SRY-related high-mobility-group box 4 (SOX4).[136] These studies collectively highlight the influence of lncRNAs on the miRNA/EMT axis in CC cells. LncRNAs have the potential to serve as biomarkers for CC diagnosis or as potential targets for CC treatment. However, the relationship between lncRNAs, miRNAs, and the regulation of EMT in CC is dynamic and complex. Further research is needed to validate the association between lncRNAs and the miRNA/EMT axis, unraveling this intriguing connection.

CircRnas as main regulators

Both circRNAs and lncRNAs belong to non-coding RNAs and exhibit similar regulatory effects on miRNAs. As oncogenes, circRNAs promote the EMT process. For example, circ-0033550, renamed as that circular RNAs-serine/threonine kinase 1 (circ-AKT1), targets miR-942–5p.[137] CircRNA_PVT1 targets miR-1286.[138] Circular RNA homeodomain interacting protein kinase 3 (Circ-HIPK3) acts as a competitive endogenous RNA for miR-338–3p.[139] circRNA MOTL1 (CircAMOTL1) regulates salt-inducible kinase 2 (SIK2) expression through sponge binding to miR-526b.[140] circRNA GSE1 (CircGSE1) interacts with miR-138–5p.[141] As tumor suppressor genes inhibiting the EMT process, circRNA UBAP2 (CircUBAP2) loss regulates SOX4 by disrupting the ceRNA function of miR361–3p.[142] Circ-MYBL2 directly inhibits the target miR-361–3p.[143] Due to the excellent stability of circRNAs, they can be detected in various body fluids. This unique advantage makes circRNAs potential biomarkers and important targets for CC diagnosis, treatment, and monitoring.

CONCLUSIONS AND FUTURE DIRECTIONS

Recent years, miRNAs have gained significant attention as therapeutic targets and biomarkers in tumor malignant. An increasing number of studies have shown that disturblanced miRNAs in cancer act as onco-suppressor genes or oncogenes in CC. On the other hand, studies have shown that EMT can act as a target of miRNAs in CC. Incraseing evidences have proved that miRNAs could influence the malignant activity of CC through modulating EMT which could promote metastasis and migration of CC cells. In present review, we provided a comprehensive review on role of miRNAs in regulation of EMT in CC cells and discussed the EMT process and its transcription factors, how miRNA inhibite and induce the EMT process, miRNA influence the chemecosesitive by influence the EMT process and the regulations of miRNA and EMT. Several signaling pathways were listed to show that miRNAs could function as critical players in regulating EMT process in CC. These miRNAs and their regulaters could be considered as promising candidates in the diagnosis and treatment of CC.

DECLARATION

Author contributions

Wu SY: wrote the manuscrip. Wang DY drew the figures. Wang C participated in discussions on the manuscript. Jin P: Supervision. Xu TM: Supervision, Project administration.

Ethics approval

Not applicable.

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Conflict of interest

Xu TM is an editorial board member of the journal. The article as subject to the journal's standard procedures.

Data availability statement

Not additional data.

REFERENCES

1. Monk BJ, Tan DSP, Hernández Chagüi JD, *et al.* Proportions and incidence of locally advanced cervical cancer: a global systematic literature review. *Int J Gynecol Cancer.* 2022;32(12):1531–1539.
2. Shintani Y, Maeda M, Chaika N, Johnson KR, Wheelock MJ. Collagen I promotes epithelial-to-mesenchymal transition in lung cancer cells *via* transforming growth factor-beta signaling. *Am J Respir Cell Mol Biol.* 2008;38(1):95–104.
3. Romeo E, Caserta CA, Rumio C, Marcucci F. The vicious cross-talk between tumor cells with an EMT phenotype and cells of the immune system. *Cells.* 2019;8(5):460.
4. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. *J Clin Invest.* 2009;119(6):1420–1428.
5. Duband JL, Monier F, Delannet M, Newgreen D. Epithelium-mesenchyme transition during neural crest development. *Acta Anat (Basel).* 1995;154(1):63–78.
6. Griffith CM, Hay ED. Epithelial-mesenchymal transformation during palatal fusion: carboxyfluorescein traces cells at light and electron microscopic levels. *Development.* 1992;116(4):1087–1099.
7. Bolender DL, Markwald RR. Epithelial-mesenchymal transformation in chick atrioventricular cushion morphogenesis. *Scan Electron Microsc* 1979(3):313–321.
8. Mayadev JS, Ke G, Mahantshetty U, Pereira MD, Tarnawski R, Toita T. Global challenges of radiotherapy for the treatment of locally advanced cervical cancer. *Int J Gynecol Cancer.* 2022;32(3):436–445.
9. Permuth-Wey J, Thompson RC, Burton Nabors L, *et al.* A functional polymorphism in the pre-miR-146a gene is associated with risk and prognosis in adult glioma. *J Neurooncol.* 2011;105(3):639–646.
10. Alles J, Fehlmann T, Fischer U , *et al.* An estimate of the total number of true human miRNAs. *Nucleic Acids Res.* 2019;47(7):3353–3364.
11. Salarinia R, Sahebkar A, Peyvandi M, *et al.* Epi-drugs and epi-miRs: moving beyond current cancer therapies. *Curr Cancer Drug Targets.* 2016;16(9):773–788.
12. Cano A, Pérez-Moreno MA, Rodrigo I, *et al.* The transcription factor snail controls epithelial-mesenchymal transitions by repressing E-cadherin expression. *Nat Cell Biol.* 2000;2(2):76–83.
13. Yang J, Weinberg RA. Epithelial-mesenchymal transition: at the crossroads of development and tumor metastasis. *Dev Cell.* 2008;14(6):818–829.
14. de Freitas Junior JCM, Morgado-Díaz JA. The role of N-glycans in colorectal cancer progression: potential biomarkers and therapeutic applications. *Oncotarget.* 2016;7(15):19395–19413.
15. Cao Q, Yu J, Dhanasekaran SM, *et al.* Repression of E-cadherin by the polycomb group protein EZH_2 in cancer. *Oncogene.* 2008;27(58):7274–7284.
16. Wang B, Tan Z, Guan F. Tumor-derived exosomes mediate the instability of cadherins and promote tumor progression. *Int J Mol Sci.* 2019;20(15):3652.
17. de Villiers EM, Fauquet C, Broker TR, Bernard HU, zur Hausen H. Classification of papillomaviruses. *Virology.* 2004;324(1):17–27.
18. Hellner K, Mar J, Fang F, Quackenbush J, Münger K. HPV16 E7 oncogene expression in normal human epithelial cells causes molecular changes indicative of an epithelial to mesenchymal transition. *Virology.* 2009;391(1):57–63.
19. Watson RA, Thomas M, Banks L, Roberts S. Activity of the human papillomavirus E6 PDZ-binding motif correlates with an enhanced morphological transformation of immortalized human keratinocytes. *J Cell Sci.* 2003;116(Pt 24):4925–4934.
20. Mayer A, Höckel M, Schlischewsky N, Schmidberger H, Horn LC, Vaupel P. Lacking hypoxia-mediated downregulation of E-cadherin in cancers of the uterine cervix. *Br J Cancer.* 2013;108(2):402–408.
21. Wang J, Yue X. Role and importance of the expression of transcription factor FOXC2 in cervical cancer. *Oncol Lett.* 2017;14(6):6627–31.
22. Tian Y, Qi P, Niu Q, Hu X. Combined snail and E-cadherin predicts overall survival of cervical carcinoma patients: comparison among various epithelial-mesenchymal transition proteins. *Front Mol Biosci.* 2020;7:22.
23. Shah AN, Summy JM, Zhang J, Park SI, Parikh NU, Gallick GE. Development and characterization of gemcitabine-resistant pancreatic tumor cells. *Ann Surg Oncol.* 2007;14(12):3629–3637.
24. Alonso-Alconada L, Muinelo-Romay L, Madissoo K, *et al.* Molecular profiling of circulating tumor cells links plasticity to the metastatic process in endometrial cancer. *Mol Cancer.* 2014;13(1):223.
25. Tomao F, Papa A, Strudel M, *et al.* Investigating molecular profiles of ovarian cancer: an update on cancer stem cells. *J Cancer.* 2014;5(5):301–310.
26. Dima M, Pecce V, Biffoni M, *et al.* Molecular profiles of cancer stem-like cell populations in aggressive thyroid cancers. *Endocrine.* 2016;53(1):145–156.
27. Mani SA, Guo W, Liao MJ, *et al.* The epithelial-mesenchymal transition generates cells with properties of stem cells. *Cell.* 2008;133(4):704–715.
28. Lin J, Liu X, Ding D. Evidence for epithelial-mesenchymal transition in cancer stem-like cells derived from carcinoma cell lines of the cervix uteri. *Int J Clin Exp Pathol.* 2015;8(1):847–855.
29. Cao H, Yang CS, Rana TM. Evolutionary emergence of microRNAs in human embryonic stem cells. *PLoS One.* 2008;3(7):e2820.
30. Lagos-Quintana M, Rauhut R, Yalcin A, Meyer J, Lendeckel W, Tuschl T. Identification of tissue-specific microRNAs from mouse. *Curr Biol.* 2002;12(9):735–739.
31. Long MJ, Wu FX, Li P, Liu M, Li X, Tang H. MicroRNA-10a targets CHL1 and promotes cell growth, migration and invasion in human cervical cancer cells. *Cancer Lett.* 2012;324(2):186–196.
32. Xu XM, Wang XB, Chen MM, *et al.* RETRACTED: microRNA-19a and-19b regulate cervical carcinoma cell proliferation and invasion by targeting CUL5. *Cancer Lett.* 2012;322(2):148–158.
33. Khani P, Nasri F, Khani Chamani F, *et al.* Genetic and epigenetic contribution to astrocytic gliomas pathogenesis. *J Neurochem.* 2019;148(2):188–203.
34. Rahimian N, Razavi ZS, Aslanbeigi F, *et al.* Non-coding RNAs related to angiogenesis in gynecological cancer. *Gynecol Oncol.* 2021;161(3):896–912.
35. Shabaninejad Z, Yousefi F, Movahedpour A, *et al.* Electrochemical-based biosensors for microRNA detection: Nanotechnology comes into view. *Anal Biochem.* 2019;581:113349.
36. Mohammadi M, Goodarzi M, Jaafari MR, Mirzaei HR, Mirzaei H. Circulating microRNA: a new candidate for diagnostic biomarker in neuroblastoma. *Cancer Gene Ther.* 2016;23(11):371–372.
37. Movahedpour A, Ahmadi N, Ghasemi Y, Savardashtaki A, Shabaninejad Z. Circulating microRNAs as potential diagnostic biomarkers and therapeutic targets in prostate cancer: current status and future perspectives. *J Cell Biochem.* 2019;120(10):16316–16329.
38. Grimolizzi F, Monaco F, Leoni F, *et al.* Exosomal miR-126 as a circulating biomarker in non-small-cell lung cancer regulating cancer progression. *Sci Rep.* 2017;7(1):15277.
39. Hashemian SM, Pourhanifeh MH, Fadaei S, Velayati AA, Mirzaei H, Hamblin MR. Non-coding RNAs and exosomes: their role in the pathogenesis of sepsis. *Mol Ther Nucleic Acids.* 2020;21:51–74.
40. Hashemipour M, Boroumand H, Mollazadeh S, *et al.* Exosomal microRNAs and exosomal long non-coding RNAs in gynecologic

cancers. *Gynecol Oncol.* 2021;161(1):314–327.

41. Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. *Nat Rev Mol Cell Biol.* 2014;15(3):178–196.
42. Saitoh M, Endo K, Furuya S, *et al.* STAT3 integrates cooperative Ras and TGF-β signals that induce Snail expression. *Oncogene.* 2016;35(8):1049–1057.
43. Yang J, Mani SA, Donaher JL, *et al.* Twist, a master regulator of morphogenesis, plays an essential role in tumor metastasis. *Cell.* 2004;117(7):927–939.
44. Nahand JS, Vandchali NR, Darabi H, *et al.* Exosomal microRNAs: novel players in cervical cancer. *Epigenomics.* 2020;12(18):1651–1660.
45. Qiao J, Li M, Sun D, Li W, Xin Y. Knockdown of ROS proto-oncogene 1 inhibits migration and invasion in gastric cancer cells by targeting the PI3K/Akt signaling pathway. *Onco Targets Ther.* 2019;12:8569–8582.
46. Fan Q, Qiu MT, Zhu Z, *et al.* Twist induces epithelial-mesenchymal transition in cervical carcinogenesis by regulating the TGF-β/Smad3 signaling pathway. *Oncol Rep.* 2015;34(4):1787–1794.
47. Li JP, Liu Y, Yin YH. ARHGAP1 overexpression inhibits proliferation, migration and invasion of C-33A and SiHa cell lines. *Onco Targets Ther.* 2017;10:691–701.
48. Pasquier J, Abu-Kaoud N, Al Thani H, Rafii A. Epithelial to mesenchymal transition in a clinical perspective. *J Oncol.* 2015;2015:792182.
49. Sun Z, Zhang D, Cui Y, Cheng L, Cao J, Wu X. Research on chemotherapy efficacy of twist gene on cervical cancer cells to paclitaxel. *Pak J Pharm Sci.* 2014;27(5 Suppl):1713–1718. [PMID:25262524]
50. Fang YY, Tan MR, Zhou J, *et al.* MiR-214–3p inhibits epithelial-to-mesenchymal transition and metastasis of endometrial cancer cells by targeting TWIST1. *Onco Targets Ther.* 2019;12:9449–9458.
51. Zhu X, Shen H, Yin X, *et al.* MiR-186 regulation of Twist1 and ovarian cancer sensitivity to cisplatin. *Oncogene.* 2016;35(3):323–332.
52. Hu J, Gui Y, Xie P, Li G. [MicroRNA-33a regulates the invasion of cervical cancer cells *via* targeting Twist1]. *Zhong Nan Da Xue Xue Bao Yi Xue Ban.* 2015;40(10):1060–1067.
53. 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.* 2017;8(12):3220.
54. Ha GH, Kim JL, Breuer EK. TACC3 is essential for EGF-mediated EMT in cervical cancer. *PLoS One.* 2013;8(8):e70353.
55. Pang T, Li M, Zhang Y, *et al.* Y box-binding protein 1 promotes epithelial-mesenchymal transition, invasion, and metastasis of cervical cancer *via* enhancing the expressions of snail. *Int J Gynecol Cancer.* 2017;27(8):1753–1760.
56. Cui N, Yang WT, Zheng PS. Slug inhibits the proliferation and tumor formation of human cervical cancer cells by up-regulating the p21/p27 proteins and down-regulating the activity of the Wnt/β-catenin signaling pathway *via* the trans-suppression Akt1/p-Akt1 expression. *Oncotarget.* 2016;7(18):26152–26167.
57. Kumarswamy R, Mudduluru G, Ceppi P, *et al.* MicroRNA-30a inhibits epithelial-to-mesenchymal transition by targeting Snai1 and is downregulated in non-small cell lung cancer. *Int J Cancer.* 2012;130(9):2044–2053.
58. Siemens H, Jackstadt R, Hünten S, *et al.* MiR-34 and SNAIL form a double-negative feedback loop to regulate epithelial-mesenchymal transitions. *Cell Cycle.* 2011;10(24):4256–4271.
59. 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.
60. Liao H, Bai Y, Qiu S, *et al.* MiR-203 downregulation is responsible for chemoresistance in human glioblastoma by promoting epithelial-mesenchymal transition *via* SNAI2. *Oncotarget.* 2015;6(11):8914–8928.
61. Ang L, Zheng L, Wang J, *et al.* Expression of and correlation between BCL6 and ZEB family members in patients with breast cancer. *Exp Ther Med.* 2017;14(5):3985–3992.
62. Hu Y, Xie H, Liu Y, Liu W, Liu M, Tang H. MiR-484 suppresses proliferation and epithelial-mesenchymal transition by targeting ZEB1 and SMAD2 in cervical cancer cells. *Cancer Cell Int.* 2017;17:36.
63. Chen XJ, Deng YR, Wang ZC, *et al.* Hypoxia-induced ZEB1 promotes cervical cancer progression *via* CCL8-dependent tumour-associated macrophage recruitment. *Cell Death Dis.* 2019;10(7):508.
64. Chen Z, Li S, Huang K, *et al.* The nuclear protein expression levels of SNAI1 and ZEB1 are involved in the progression and lymph node metastasis of cervical cancer *via* the epithelial-mesenchymal transition pathway. *Hum Pathol.* 2013;44(10):2097–2105.
65. Li L, Han LY, Yu M, Zhou Q, Xu JC, Li P. Pituitary tumor-transforming gene 1 enhances metastases of cervical cancer cells through miR-3666-regulated ZEB1. *Tumour Biol.* 2015;37(12):15567–15573.
66. Zhao W, Wang H, Han X, *et al.* ΔNp63α attenuates tumor aggressiveness by suppressing miR-205/ZEB1-mediated epithelial-mesenchymal transition in cervical squamous cell carcinoma. *Tumour Biol.* 2016;37(8):10621–10632.
67. Wang Y, Dong X, Hu B, Wang XJ, Wang Q, Wang WL. The effects of Micro-429 on inhibition of cervical cancer cells through targeting ZEB1 and CRKL. *Biomed Pharmacother.* 2016;80:311–321.
68. Sun J, Wang S, Liu P, Liu Y. *MiR-139–5p-ZEB1* is a molecular regulator of growth, invasion, and epithelial-to-mesenchymal transition of cervical cancer. *Cancer Manag Res.* 2020;12:12723–12733.
69. Chen M, Liu LX. MiR-525–5p repressed metastasis and anoikis resistance in cervical cancer *via* blocking UBE2C/ZEB1/2 signal axis. *Dig Dis Sci.* 2020;65(8):2442–2451.
70. Li YJ, Wang Y, Wang YY. MicroRNA-99b suppresses human cervical cancer cell activity by inhibiting the PI3K/AKT/mTOR signaling pathway. *J Cell Physiol.* 2019;234(6):9577–9591.
71. Teng P, Jiao Y, Hao M, Tang X. MicroRNA-383 suppresses the PI3K-AKT-MTOR signaling pathway to inhibit development of cervical cancer *via* down-regulating PARP2. *J Cell Biochem.* 2018;119(7):5243–5252.
72. Song L, Liu S, Zhang L, *et al.* MiR-21 modulates radiosensitivity of cervical cancer through inhibiting autophagy *via* the PTEN/Akt/HIF-1α feedback loop and the Akt-mTOR signaling pathway. *Tumour Biol.* 2016;37(9):12161–12168.
73. Wang F, Tan WH, Liu W, *et al.* Effects of miR-214 on cervical cancer cell proliferation, apoptosis and invasion *via* modulating PI3K/AKT/mTOR signal pathway. *Eur Rev Med Pharmacol Sci.* 2018;22(7):1891–1898.
74. Lu R, Yang Z, Xu G, Yu S. MiR-338 modulates proliferation and autophagy by PI3K/AKT/mTOR signaling pathway in cervical cancer. *Biomed Pharmacother.* 2018;105:633–644.
75. Zhang L, Wu J, Ling M, Zhao L, Zhao K. The role of the PI3K/Akt/mTOR signalling pathway in human cancers induced by infection with human papillomaviruses. *Mol cancer.* 2015;14:87.
76. Owusu-Brackett N, Shariati M, Meric-Bernstam F. Role of PI3K/AKT/mTOR in cancer signaling. *Predict Biomark Oncol.* 2019:263–270.
77. Rashmi R, DeSelm C, Helms C, *et al.* AKT inhibitors promote cell death in cervical cancer through disruption of mTOR signaling and glucose uptake. *PLoS One.* 2014;9(4):e92948.
78. Li YM, Li XJ, Yang HL, Zhang YB, Li JC. MicroRNA-23b suppresses cervical cancer biological progression by directly targeting six1 and affecting epithelial-to-mesenchymal transition and AKT/mTOR signaling pathway. *Eur Rev Med Pharmacol Sci.* 2019;23(11):4688–4697.
79. Huang C, Qin X, Zhao N, Jin H, Zhang S, Yang H. MicroRNA-100 functions as a tumor suppressor in cervical cancer *via* downregulating the SATB1 expression and regulating AKT/mTOR signaling pathway and epithelial-to-mesenchymal transition. *Oncol Lett.* 2020;20(2):1336–1344.
80. Yang X, Feng KX, Li H, Wang L, Xia H. MicroRNA-199a inhibits cell proliferation, migration, and invasion and activates AKT/mTOR

signaling pathway by targeting B7-H3 in cervical cancer. *Technol Cancer Res Treat.* 2020;19:1533033820942245.

81. Bagherian A, Mardani R, Roudi B, *et al.* Combination therapy with nanomicellar-curcumin and temozolomide for *in vitro* therapy of glioblastoma multiforme *via* Wnt signaling pathways. *J Mol Neurosci.* 2020;70(10):1471–1483.
82. Li B, Guo X, Li N, *et al.* WNT1, a target of miR-34a, promotes cervical squamous cell carcinoma proliferation and invasion by induction of an E-P cadherin switch *via* the WNT/β-catenin pathway. *Cell Oncol (Dordr).* 2020;43(3):489–503.
83. Deng B, Zhang Y, Zhang S, Wen F, Miao Y, Guo K. MicroRNA-142–3p inhibits cell proliferation and invasion of cervical cancer cells by targeting FZD7. *Tumour Biol.* 2015;36(10):8065–8073.
84. Cauchi S, Froguel P. TCF7L2 genetic defect and type 2 diabetes. *Curr Diab Rep.* 2008;8(2):149–155.
85. Zhou C, Tan DM, Chen L, *et al.* Effect of miR-212 targeting TCF7L2 on the proliferation and metastasis of cervical cancer. *Eur Rev Med Pharmacol Sci.* 2017;21(2):219–226.
86. Wang X, Xia Y. MicroRNA-328 inhibits cervical cancer cell proliferation and tumorigenesis by targeting TCF7L2. *Biochem Biophys Res Commun.* 2016;475(2):169–175.
87. Li Q, Yu X, Yang L. MiR-145 inhibits cervical cancer progression and metastasis by targeting WNT2B by Wnt/β-catenin pathway. *Int J Clin Exp Pathol.* 2019;12(10):3740–3751.
88. Miao H, Wang N, Shi LX, Wang Z, Song WB. Overexpression of mircoRNA-137 inhibits cervical cancer cell invasion, migration and epithelial-mesenchymal transition by suppressing the TGF-β/smad pathway *via* binding to GREM1. *Cancer Cell Int.* 2019;19:147.
89. Yang S, Sun Y, Jiang D, *et al.* MiR-362 suppresses cervical cancer progression *via* directly targeting BAP31 and activating TGFβ/Smad pathway. *Cancer Med.* 2021;10(1):305–316.
90. Liu X, Zhou Y, Ning YE, Gu H, Tong Y, Wang N. MiR-195–5p inhibits malignant progression of cervical cancer by targeting YAP1. *Onco Targets Ther.* 2020;13:931–944.
91. Qu ZY, Cui GY, Shi PJ, Wang HQ. Potential suppressive functions of microRNA-504 in cervical cancer cells malignant process were achieved by targeting PAICS and regulating EMT. *Arch Gynecol Obstet.* 2020;302(1):173–82.
92. Zhang XY, Dong XM, Wang FP. MiR-377–3p inhibits cell metastasis and epithelial-mesenchymal transition in cervical carcinoma through targeting SGK3. *Eur Rev Med Pharmacol Sci.* 2020;24(9):4687–4696.
93. Li J, Wang B, Feng Y, Wang T, Wang S, Wu M. Sema4C mediates EMT inducing chemotherapeutic resistance of miR-31–3p in cervical cancer cells. *Sci Rep.* 2019;9(1):17727.
94. Li H, Wang J, Xu F, *et al.* By downregulating PBX3, miR-526b suppresses the epithelial-mesenchymal transition process in cervical cancer cells. *Future Oncol.* 2019;15(14):1577–1591.
95. Jiang Z, Song Q, Zeng R, *et al.* MicroRNA-218 inhibits EMT, migration and invasion by targeting SFMBT1 and DCUN1D1 in cervical cancer. *Oncotarget.* 2016;7(29):45622–45636.
96. Sathyanarayanan A, Chandrasekaran KS, Karunagaran D. MicroRNA-145 modulates epithelial-mesenchymal transition and suppresses proliferation, migration and invasion by targeting SIP1 in human cervical cancer cells. *Cell Oncol (Dordr).* 2017;40(2):119–131.
97. Cheng YX, Chen GT, Chen C, *et al.* MicroRNA-200b inhibits epithelial-mesenchymal transition and migration of cervical cancer cells by directly targeting RhoE. *Mol Med Rep.* 2016;13(4):3139–3146.
98. Feng J. Upregulation of microRNA-4262 targets kaiso (ZBTB33) to inhibit the proliferation and EMT of cervical cancer cells. *Oncol Res.* 2018;26(8):1215–1225.
99. Xu D, Dong P, Xiong Y, *et al.* MicroRNA-361-mediated inhibition of HSP90 expression and EMT in cervical cancer is counteracted by oncogenic lncRNA NEAT1. *Cells.* 2020;9(3):632.
100. Zhang X, Cai D, Meng L, Wang B. MicroRNA-124 inhibits proliferation, invasion, migration and epithelial-mesenchymal transition of cervical carcinoma cells by targeting astrocyte-elevated gene-1. *Oncol Rep.* 2016;36(4):2321–2328.
101. Zhang M, Xu Q, Yan S, Li Z, Yan W, Jia X. Suppression of forkhead box Q1 by microRNA-506 represses the proliferation and epithelial-mesenchymal transition of cervical cancer cells. *Oncol Rep.* 2016;35(5):3106–3114.
102. Xu D, Liu S, Zhang L, Song L. MiR-211 inhibits invasion and epithelial-to-mesenchymal transition (EMT) of cervical cancer cells *via* targeting MUC4. *Biochem Biophys Res Commun.* 2017;485(2):556–562.
103. Zhang P, Hou Q, Yue Q. MiR-204–5p/TFAP2A feedback loop positively regulates the proliferation, migration, invasion and EMT process in cervical cancer. *Cancer Biomark.* 2020;28(3):381–390.
104. Huang Y, Huang H, Li M, Zhang X, Liu Y, Wang Y. MicroRNA-374c-5p regulates the invasion and migration of cervical cancer by acting on the Foxc1/snail pathway. *Biomed Pharmacother.* 2017;94:1038–1047.
105. Wang Z, He S, Guo P, Guo X, Zheng J. MicroRNA-1297 inhibits metastasis and epithelial-mesenchymal transition by targeting AEG-1 in cervical cancer. *Oncol Rep.* 2017;38(5):3121–3129.
106. Feng J, Wang T. MicroRNA-873 serves a critical role in human cervical cancer proliferation and metastasis *via* regulating glioma-associated oncogene homolog 1. *Exp Ther Med.* 2020;19(2):1243–1250.
107. Yang Z, Sun Q, Guo J, *et al.* GRSF1-mediated MIR-G-1 promotes malignant behavior and nuclear autophagy by directly upregulating TMED5 and LMNB1 in cervical cancer cells. *Autophagy.* 2019;15(4):668–685.
108. Wu X, Xi X, Yan Q, *et al.* MicroRNA-361–5p facilitates cervical cancer progression through mediation of epithelial-to-mesenchymal transition. *Med Oncol.* 2013;30(4):751.
109. Pang Y, Mao SS, Yao R, *et al.* TGF-β induced epithelial-mesenchymal transition in an advanced cervical tumor model by 3D printing. *Biofabrication.* 2018;10(4):044102.
110. Zhou JY, Zheng SR, Liu J, Shi R, Yu HL, Wei M. MiR-519d facilitates the progression and metastasis of cervical cancer through direct targeting Smad7. *Cancer Cell Int.* 2016;16:21.
111. Frank AC, Ebersberger S, Fink AF, *et al.* Apoptotic tumor cell-derived microRNA-375 uses CD36 to alter the tumor-associated macrophage phenotype. *Nat Commun.* 2019;10(1):1135.
112. Xiong Y, Sun F, Dong P, *et al.* iASPP induces EMT and cisplatin resistance in human cervical cancer through miR-20a-FBXL5/BTG3 signaling. *J Exp Clin Cancer Res.* 2017;36(1):48.
113. Zhao S, Yao DS, Chen JY, Ding N. Aberrant expression of miR-20a and miR-203 in cervical cancer. *Asian Pac J Cancer Prev.* 2013;14(4):2289–2293.
114. 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.
115. Zhu J, Han S. MiR-150–5p promotes the proliferation and epithelial-mesenchymal transition of cervical carcinoma cells *via* targeting SRCIN1. *Pathol Res Pract.* 2019;215(4):738–747.
116. Yao J, Deng B, Zheng L, Dou L, Guo Y, Guo K. MiR-27b is upregulated in cervical carcinogenesis and promotes cell growth and invasion by regulating CDH11 and epithelial-mesenchymal transition. *Oncol Rep.* 2016;35(3):1645–1651.
117. Piao J, You K, Guo Y, Zhang Y, Li Z, Geng L. Substrate stiffness affects epithelial-mesenchymal transition of cervical cancer cells through miR-106b and its target protein DAB2. *Int J Oncol.* 2017;50(6):2033–2042.[PMID: 28498390 DOI: 10.3892/ijo.2017.397
118. Shen Y, Wang P, Li Y, *et al.* MiR-375 is upregulated in acquired paclitaxel resistance in cervical cancer. *Br J Cancer.* 2013;109(1):92–99.
119. Shen Y, Zhou J, Li Y, *et al.* MiR-375 mediated acquired chemo-resistance in cervical cancer by facilitating EMT. *PLoS One.* 2014;9(10):e109299.
120. Song L, Liu S, Zeng S, Zhang L, Li X. MiR-375 modulates radiosensitivity of HR-HPV-positive cervical cancer cells by targeting

UBE3A through the p53 pathway. *Med Sci Monit.* 2015;21:2210–2217.

121. Liu Q, Liu S, Wang D. Overexpression of microRNA-21 decreased the sensitivity of advanced cervical cancer to chemoradiotherapy through SMAD7. *Anticancer Drugs.* 2020;31(3):272–281.
122. Lei C, Wang Y, Huang Y, *et al.* Up-regulated miR155 reverses the epithelial-mesenchymal transition induced by EGF and increases chemo-sensitivity to cisplatin in human Caski cervical cancer cells. *PLoS One.* 2012;7(12):e52310.
123. Song J, Li Y. MiR-25–3p reverses epithelial-mesenchymal transition *via* targeting Sema4C in cisplatin-resistance cervical cancer cells. *Cancer Sci.* 2017;108(1):23–31.
124. Tong R, Zhang J, Wang C, Li Q, Wang L, Ju M. Inhibition of miR-574–5p suppresses cell growth and metastasis and enhances chemosensitivity by targeting RNA binding protein QKI in cervical cancer cells. *Naunyn Schmiedebergs Arch Pharmacol.* 2020;393(6):951–966.
125. Shafabakhsh R, Arianfar F, Vosough M, *et al.* Autophagy and gastrointestinal cancers: the behind the scenes role of long non-coding RNAs in initiation, progression, and treatment resistance. *Cancer Gene Ther.* 2021;28:1229–1255.
126. Razavi ZS, Tajiknia V, Majidi S, *et al.* Gynecologic cancers and non-coding RNAs: Epigenetic regulators with emerging roles. *Crit Rev Oncol Hematol.* 2021;157:103192.
127. Shen CJ, Cheng YM, Wang CL. LncRNA PVT1 epigenetically silences miR-195 and modulates EMT and chemoresistance in cervical cancer cells. *J Drug Target.* 2017;25(7):637–644.
128. Liu H, Zhang L, Ding X, Sui X. LINC00861 inhibits the progression of cervical cancer cells by functioning as a ceRNA for miR□ 513b□ 5p and regulating the PTEN/AKT/mTOR signaling pathway. *Mol Med Rep.* 2021;23(1):24.
129. Fan Y, Sheng W, Meng Y, Cao Y, Li R. LncRNA PTENP1 inhibits cervical cancer progression by suppressing miR-106b. *Artif Cells Nanomed Biotechnol.* 2020;48(1):393–407.
130. Tong R, Zhang J, Wang C, Li X, Yu T, Wang L. LncRNA PTCSC3 inhibits the proliferation, invasion and migration of cervical cancer cells *via* sponging miR-574–5p. *Clin Exp Pharma Physio.* 2020;47(3):439–448.
131. Fan MJ, Zou YH, He PJ, Zhang S, Sun XM, Li CZ. Long non-coding RNA *SPRY4-IT1* promotes epithelial-mesenchymal transition of cervical cancer by regulating the miR-101–3p/ZEB1 axis. *Biosci Rep.* 2019;39(6):BSR20181339.
132. Yang TJ, Wang L, Zhang Y, Zheng JD, Liu L. LncRNA UCA1 regulates cervical cancer survival and EMT occurrence by targeting miR-155. Eur Rev Med Pharmacol Sci. 2020 Oct;24(19):9869–9879.
133. Feng S, Liu W, Bai X, *et al.* LncRNA-CTS promotes metastasis and epithelial-to-mesenchymal transition through regulating miR-505/ZEB2 axis in cervical cancer. *Cancer Lett.* 2019;465:105–117.
134. Liang H, Zhang C, Guan H, Liu J, Cui Y. LncRNA DANCR promotes cervical cancer progression by upregulating ROCK1 *via* sponging miR-335–5p. *J Cell Physiol.* 2019;234(5):7266–7278.
135. Feng Y, Ma J, Fan H, *et al.* TNF-α-induced lncRNA LOC105374902 promotes the malignant behavior of cervical cancer cells by acting as a sponge of miR-1285–3p. *Biochem Biophys Res Commun.* 2019;513(1):56–63.
136. Guo M, Lin B, Li G, Lin J, Jiang X. LncRNA TDRG1 promotes the proliferation, migration, and invasion of cervical cancer cells by sponging miR-214–5p to target SOX4. *J Recept Signal Transduct.* 2020;40(3):281–293.
137. Ou R, Mo L, Tang H, *et al.* circRNA-AKT1 sequesters miR-942–5p to upregulate AKT1 and promote cervical cancer progression. *Mol Ther Nucleic Acids.* 2020;20:308–322.
138. Wang H, Wei M, Kang Y, Xing J, Zhao Y. Circular RNA circ_PVT1 induces epithelial-mesenchymal transition to promote metastasis of cervical cancer. *Aging (Albany NY).* 2020;12(20):20139–20151.
139. Qian W, Huang T, Feng W. Circular RNA HIPK3 promotes EMT of cervical cancer through sponging miR-338–3p to up-regulate HIF-1α. *Cancer Manag Res.* 2020;12:177–187.
140. Sun Z, Niu S, Xu F, Zhao W, Ma R, Chen M. CircAMOTL1 promotes tumorigenesis through miR-526b/SIK2 axis in cervical cancer. *Front Cell Dev Biol.* 2020;8:568190.
141. Fan S, Zhao S, Gao X, *et al.* Circular RNA circGSE1 promotes cervical cancer progression through miR-138–5p/vimentin. *Onco Targets Ther.* 2020;13:13371–13386.
142. Meng L, Jia X, Yu W, Wang C, Chen J, Liu F. Circular RNA UBAP2 contributes to tumor growth and metastasis of cervical cancer *via* modulating miR-361–3p/SOX4 axis. *Cancer Cell Int.* 2020;20:357.
143. Wang J, Li H, Liang Z. Circ-MYBL2 serves As A sponge for miR-361–3p promoting cervical cancer cells proliferation and invasion. *Onco Targets Ther.* 2019;12:9957–9964.