Abstract

Although as a potentially preventable disease, Cervical Cancer (CC) is the second most commonly diagnosed gynecological cancer and with an approximate more than 529,000 new cases annually around the world. As a group of small non-coding RNAs with 18 to 25 nucleotides, by repressing translation or inducing mRNA cleavage or degradation, microRNAs (miRNAs) regulate circa one-third of all human genes including genes involved in diverse important cellular processes, including cell cycle, proliferation, differentiation, and apoptosis. Extensive evidence showed that misexpression of miRNAs is closely related to the onset and progression of CC. This review will provide an overview of the function of miRNAs in cervical cancer and their mechanisms involved in cervical carcinogenesis.

Keywords: miRNA; Cervical cancer; Proliferation; Diagnosis; Metastasis; Invasion; Radio resistance; Chemo resistance

Abbreviations

CC: Cervical Cancer; MiRNA: MicroRNA; PAP test: Papanicolaou test; RT-PCR: Real time polymerase chain reaction; FIGO stage: International federation of gynecology and obstetrics stage; XIAP: X-linked inhibitor of apoptosis protein; EGFR: Epidermal growth factor receptor; PDCD4: Programmed cell death 4; PTEN: Phosphate and tension homology deleted on chromosome ten; FOXO1: Fork head box protein O1; FOXO3a: Fork head box protein O3a; RECK: Reversion-inducing-cyste-inc-rich protein with kazal motifs; EphrinA5: Eph family receptor interacting proteins A5; SAMD9: Sterile alpha motif domain-containing 9; PTPN9: Protein tyrosine phosphatase: non-receptor type 9; NF-kB: Nuclear factor-kB; PKB: Protein kinase B; TNF-α: Tumor necrosis factor-α; E2F1: E2F transcription factor 1; YAP: Yes-associated protein; TFCP2: Transcription factor CP2; Bcl-2: B-cell lymphoma-2; HIP-1a: Hypoxia-inducible factor-1α; LKB1: Liver kinase B1; YOD1: Yeast OTU deubiquitinating enzyme 1 homolog; VEGF-A: Vascular endothelial growth factor C; FOXO4: Fork head box protein O4; GIT1: G-protein-coupled receptor (GPCR)-kinase interacting protein-1; HPV16 E6: Human papillomavirus 16 E6; FGF9: Fibroblast growth factor 9; PI3K: Phosphoinositide3-kinase; AKT: Protein kinase B; mTOR: Mammalian target of rapamycin; MMP9: Matrix metalloproteinease-9; MAPK4: Mitogen-activated protein kinase 4; MYB: V-myb avian myeloblastosis viral oncogene homolog; HOXB7: Homeobox-B7; HDGF: Hepatoma-derived growth factor; p-Rb: Phosphorylated retinoblastoma; PCNA: Proliferating cell nuclear antigen; TCF7L2: Transcription factor 7-like 2; Gli3: Gli family zinc finger 3; FOXQ1: Fork head box Q1; EMT: Epithelial mesenchymal transition; STAT3: Signal transducer and activator of transcription 3; KDM5B: Lysine specific demethylase 5B gene; PRL-1: Protein tyrosine phosphatase type IVA


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Publisher Name: Medtext Publications LLC

Manuscript compiled: October 03rd, 2019

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programs are expected to decrease in the incidence of CC in the test (Pap test) and Human Papilloma Virus (HPV) vaccination new cases of Cervical Cancer (CC) worldwide each year and nearly of abnormal expression of miRNAs are tightly linked to various reviewed literatures have been reported in the last decades. Hundreds of miRNAs in pathogenenesis of cancer, more than 25,000 peer-[10]. Extensive of literature have been published involving the role including development, differentiation, metabolism, immunity, cell an important role in various physiological and pathological processes Up to now, 2578 different miRNA sequences have been identified genes) concomitantly to control entire cell signaling pathways [7,8]. After then, scientific community confirmed that micro RNA represent believed that had no candid role in mediating the cellular processes [6]. Through RNA bio molecules have been found since the late 1800s, the functional activities of them have long been overshadowed by DNA and proteins. MicroRNAs, or miRNAs, are a class of non-coding RNA micro molecules of 18–25 nucleotides in length and excise in various animal and plant cells, which can post-transcriptional regulate massive target genes in organisms due to the complementarity of bases to the 3’ un translated regions (3’ UTRs) of messenger RNAs (mRNAs). Different to plant miRNAs that possess massive regions of complementarity with their target genes, animal miRNAs are just partially complementary and contain a propensity to recognize targets by 6 to 8 nt ‘seed’ sequences, normally locate at nt position 2–8 of the 5’-end of the miRNA [5]. Before the emergence of transcriptomic and high-throughput technologies, the non-coding RNA molecules were believed that had no candid role in mediating the cellular processes [6]. After then, scientific community confirmed that micro RNA represent only a small part of the genome, but they can regulate the expression of hundreds of different miRNAs (approximately 20%–30% of all human genes) concomitantly to control entire cell signaling pathways [7,8]. Up to now, 2578 different miRNA sequences have been identified and released in human in the miBase database [9]. MiRNAs play an important role in various physiological and pathological processes including development, differentiation, metabolism, immunity, cell cycle, proliferation, apoptosis, cell identity, and stem cell maintenance [10]. Extensive of literature have been published involving the role of miRNAs in pathogenenesis of cancer, more than 25,000 peer-reviewed literatures have been reported in the last decades. Hundreds of abnormal expression of miRNAs are tightly linked to various aspects of cancer biology, including proliferation, differentiation, apoptosis, migration, invasion, metastasis angiogenesis, involving most types of human cancer, such as breast, lung, colorectal, prostate, gastric, and so on; about half of all miRNA genes are evidence to be located in genomic region associated with cancer. The dysregulation is involved in cancer pathogenesis via the modulation of oncogenes being up-regulated or tumor suppressors being down-regulated in cancer [10]. Certain miRNAs may be either an oncogenes or anti oncogenes in different cancer cells [11], for example, miRNA-203 is highly expressed in pancreatic and breast cancer, but low-expressed in esophageal, prostate, and CC [12]. Moreover, the expression profiling of miRNA is quite different depending on both the histological type of the tissues and pathologic not pathologic conditions, because their expression is different between the normal tissues and cancer tissues [13], which suggests that it is necessary to research the expression of certain miRNA in specific cancer.

It is expected that comprehensive exploration of miRNAs associated with development and progression of CC will help our understanding of the molecular basis of pathogenesis, thus provide tools for early diagnosis and prognosis as well as additional therapeutic targets. This review will focus on the recent literature on the expression of miRNAs and their targeted gene in CC, the physiologic function of these miRNAs will also be summarized.  

**Application of miRNAs in diagnosis and prognosis of CC**  
Since 2007, the secreted miRNAs embedded in exosome and granular vesicles circulation in blood were found, these miRNAs have subsequently been confirmed to transfect through intercellular communication and in signal transduction through transfer via the placenta and breast milk. Using specified reagents, miRNAs are stable enough for being extracted from a broad variety of specimens, including fresh tissues, cell lines, blood, plasma, serum, and urine, and then the expression of them can be amplified and determined using quantitative RT-PCR and microarray analysis, thus miRNAs with specific expression changes in cancer can be used as diagnostic and prognostic biomarkers based on plasma and serum tests [14,15]. Different patterns of miRNA expression, even of single miRNA, have been applied in the early detection, classification, prognostic, and predictive biomarkers for cancer [16]. More and more literature has reported the application of miRNAs as cancer diagnostic marker and as anticancer therapy [17]. Tang et al. [18] assessed the expression of the miRNAs in CC using TaqMan RT-PCR, and explored the spatial expression of miRNA-182 in CC and normal cervix by in situ hybridization. As a result, 2 up-regulated (miRNA-182 and -183) and 9 down-regulated (miRNA-211, -145, -223, -150, -142-5p, -328, -195, -199b, and -142-3p) miRNAs were consistently identified in CC. Lin et al. [19] characterized the miRNA profile of CC in Uyguur women for application in early diagnosis by using miRNA microarray, RT-PCR, and locked nucleic acid in situ hybridization, found that miRNA-101 was significantly down-regulated in tissues of CC as compared with the normal ones. Li et al. [20] found that there were 195 up-regulated miRNAs and 96 down-regulated ones in CC tissues relative to normal ones, particularly for up-regulated miRNAs: miRNA-21, -10a, -15b, 20b, -141, -200a, -224; and down-regulated miRNAs: miRNA-143, -145, -203, -126. Hu et al. [21] identified 2 miRNAs (miRNA-200a and -9), which could be used to predict patient survival and played important regulatory roles in CC control. Han et al. [22] characterized the miRNA-21 and evaluated its potential as biomarker for the prognosis of CC, confirmed that the expression of miRNA-21 was associated with clinicopathological parameters, including depth of invasion and lymph node metastasis.
Yang et al. [23] found the expression level of miRNA-126 in CC tissues was lower than that in adjacent non-tumorous tissues using TaqMan quantitative RT-PCR, and its low expression was significantly associated with lymphatic invasion, distant metastasis, International Federation of Gynecology and Obstetrics stage (FIGO) stage, and histological grade. The same is miRNA-142-3p and -138 [24,25]. However, miRNA-31 is dramatically up-regulated in CC cell lines and tissues; the high miRNA-31 level was significantly related to higher FIGO stage, node metastasis, vascular involvement, and deep stromal invasion [26]. Liu et al. [27] successfully built multivariate Cox’s model by using both clinical information and miRNA expression levels of patients with CC, and figured out 7 miRNAs, which played important roles in the pathogenesis, progression, and prognosis of CC. As mentioned above, distinguishable abnormalities in several of miRNAs expression patterns have been confirmed thus make its application as a diagnostic or prognostic biomarker to be properly implemented [16].

Regulation of miRNAs in cell cycle and proliferation control in CC

Cell proliferation depends upon the regulation of cell cycle, and dysregulation of cell cycle regulators may result in cell apoptosis or abnormal proliferation [28]. (Figure 1) show the principal miRNAs involved in cell-cycle regulation in CC. The various oncogenic and tumor suppressor miRNAs discussed in this paragraph are summarized in (Table 1 and 2).

![Figure 1: A. Regulation of cell-cycle by down-regulated miRNAs in CC; B. Regulation of cell-cycle by up-regulated miRNAs in CC.](image)

**Table 1:** miRNAs involvement in cell proliferation and apoptosis in CC and their target genes.

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Expression status</th>
<th>Target gene</th>
<th>Related functions</th>
<th>Effect on apoptosis</th>
<th>miRNA</th>
<th>Status</th>
<th>Target gene</th>
<th>Related functions</th>
<th>Effect on apoptosis</th>
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<tr>
<td>miRNA-7</td>
<td>Down</td>
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<td>Promote apoptosis [29,30]</td>
<td>miRNA-433</td>
<td>Down</td>
<td>MTDH</td>
<td>Cell proliferation and apoptosis</td>
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<td>miRNA-10a-5p</td>
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<td>BDNF</td>
<td>Cell proliferation</td>
<td>Suppress cell proliferation [146]</td>
<td>miRNA-454-3p</td>
<td>Down</td>
<td>C-met</td>
<td>Cell proliferation</td>
<td>Suppress cell proliferation [130]</td>
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<td>Down</td>
<td>PRIL-1</td>
<td>Cell proliferation</td>
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<td>miRNA-484</td>
<td>Down</td>
<td>SMAD2</td>
<td>Cell proliferation, apoptosis</td>
<td>Suppress cell proliferation [131]</td>
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<td>Suppress cell proliferation [60]</td>
<td>miRNA-485</td>
<td>Down</td>
<td>MACC1</td>
<td>Cell proliferation</td>
<td>Suppress cell proliferation [132]</td>
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<td>Down</td>
<td>Cox-2</td>
<td>Cell proliferation and apoptosis</td>
<td>Suppress cell proliferation, promote apoptosis [64]</td>
<td>miRNA-486-3p</td>
<td>Down</td>
<td>ECM1</td>
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<td>Suppress cell proliferation [132]</td>
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<td>miRNA-124</td>
<td>Down</td>
<td>AEG-1/AmotL1</td>
<td>Cell proliferation</td>
<td>Suppress cell proliferation [65,66]</td>
<td>miRNA-491-5p</td>
<td>Down</td>
<td>hTERT</td>
<td>Cell proliferation and apoptosis</td>
<td>Suppress cell proliferation, promote apoptosis [134]</td>
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<td>Function</td>
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<td>miRNA-634</td>
<td>mTOR</td>
<td>Cell proliferation</td>
<td>miRNA-847</td>
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<td>miRNA-1284</td>
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<td>miRNA-let-7a</td>
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<td>miRNA-21</td>
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<td>miRNA-92</td>
<td>PTEN</td>
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<td>miRNA-9</td>
<td>FOXO3/PDCD4</td>
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<tr>
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<td>HOXB7</td>
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<td>miRNA-20a</td>
<td>TNKS2/PDCD6/ATG7/TIMP2</td>
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<td>CCND1</td>
<td>Cell proliferation</td>
<td>miRNA-31</td>
<td>ARID1A</td>
<td>Cell proliferation</td>
<td>miRNA-146a</td>
<td>-</td>
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<td>VEGFA/survivin</td>
<td>Cell proliferation</td>
<td>miRNA-146b-5p</td>
<td>CXCR4</td>
<td>Cell proliferation and apoptosis</td>
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<tr>
<td>miRNA-206</td>
<td>G6PD/Notch3</td>
<td>Cell proliferation and apoptosis</td>
<td>miRNA-124-3p</td>
<td>mTOR</td>
<td>Cell proliferation</td>
<td>miRNA-847</td>
<td>ETS1</td>
<td>Cell proliferation and apoptosis</td>
<td></td>
</tr>
</tbody>
</table>

[References: 67, 64, 136, 31,32, 212, 66,72, 142, 35,36, 143, 78, 159, 82, 54, 58, 147,148, 153-155, 157, 161, 163]
miRNA-211  Down  ZEB1  Cell proliferation  Suppress cell proliferation [108]  miRNA-196a  Up  FOXO1/p27kip1/Netrin 4  Cell proliferation  Promote proliferation [167-169]


miRNA-320  Down  FOXM1/Mcl-1  Cell proliferation and apoptosis  Suppress cell proliferation, promote apoptosis [114,115]  miRNA-205  Up  CYR61/CTGF  Cell proliferation  Promote proliferation [172]

m i R N A -329-3p  Down  MAPK1  Cell proliferation  Suppress cell proliferation [116,117]  miRNA-361-5p  Up  -  Cell proliferation  Promote proliferation [177]

m i R N A -342-3p  Down  FOXM1  Cell proliferation  Suppress cell proliferation [120]  miRNA-494  Up  Ptg1  Cell proliferation  Promote proliferation [180]

miRNA-362  Down  SIX1  Cell proliferation  Suppress cell proliferation [121]  miRNA-501  Up  CYLD  Cell proliferation and apoptosis  Promote proliferation, suppress apoptosis [181]

miRNA-377  Down  ZEB2  Cell proliferation  Suppress cell proliferation [114]  miRNA-590-5p  Up  CHL1  Cell proliferation and apoptosis  Promote proliferation [182]

miRNA-411  Down  STAT3  Cell proliferation  Suppress cell proliferation [115]  miRNA-944  Up  -  Cell proliferation  Promote proliferation [185]

miRNA-429  Down  IKKβ  Cell viability, proliferation, apoptosis  Suppress cell proliferation, promote apoptosis [116]  

| Table 2: miRNAs involvement in cell cycle in CC and their target genes. |
| miRNA  | Expression status  | Target gene  | Effect on cell cycle  | miRNA  | Expression status  | Target gene  | Effect on cell cycle  |
| miRNA-10a-5p  | Down  | BDNF  | Arrest in G1 phase [152]  | miRNA-20a  | Up  | CyclinB1/CCND1/CDK2  | Arrest in G1 phase [154]  |
| miRNA-143  | Down  | HIF-1α  | Arrest in G0/G1 phase [39]  | miRNA-92a  | Up  | FBXW7/p21  | Promoting cell cycle transition from G1 to S phase, arrest in G1 phase [159,160]  |
| miRNA-132  | Down  | CCND1  | Arrest in G1/S phase transition [71]  | miRNA-150  | Up  | FOXO4  | Promote cell turning into S phase from G0/G1 phase [162]  |
| miRNA-195  | Down  | CCND1a/pRb/PCNA  | Arrest in G1 phase [94]  | miRNA-155  | Up  | LKB1  | Arrest in G1 phase [57]  |
| miRNA-375  | Down  |  | Arrested G1/S phase transition [123]  | miRNA-196a  | Up  | FOXO1/p27kip1  | Promote cell turning into S phase from G1 phase [167]  |
| miRNA-101  | Down  | Fos  | Arrested G1/S phase transition [63]  | miRNA-494  | Up  | PTEN  | Arrest in G1 phase [180]  |
| miRNA-9  | Up  | PDCD4  | Promote cell turning into G2 phase from S phase [147]  | miRNA-390-5p  | Up  | CHL1  | Promote cell turning into S phase from G1 phase [182]  |

Down-regulated miRNAs

**MiRNA-7**: MiRNA-7, involved in various human tumors, played a tumor suppressor role and was dramatically down-regulated in CC. The protein and mRNA expression of X-linked Inhibitor of Apoptosis Protein (XIAP) and Epidermal Growth Factor Receptor (EGFR) were down-regulated by miRNA-7. Cell viability was inhibited, but cell apoptosis was induced by miRNA-7 [29,30]. The results indicated that miRNA-7 directly binded to the XIAP 3’ UTR and specifically suppressed the expression of XIAP, thus inhibited the cell viability and colony formation, but promoted the apoptosis of CC cells.

**MiRNA-130a**: MiRNA-130a was dramatically down-regulated in CC tissues as compared with adjacent non-cancerous ones, and
exhibited lower expression level (by 3-fold) in CC as compared to normal cervical ones [31]. The role of 3 elements, miRNA-130a, nuclear factor-kB (NF-kB), and Phospho and Tension homology deleted on chromosome ten (PTEN), in the development and progression of CC has been reported. MiRNA-130a promoted the proliferation of CC cells by targeting PTEN; furthermore, NF-kB activated the growth of CC cells by up-regulating miRNA-130a. In addition, miRNA-130a promoted cell growth and initiated Protein Kinase B (PKB) pathway activation by targeting PTEN 3’ untranslated region [32]. Notably, tumor necrosis factor-α (TNF-α) was identified as another target site of miRNA-130a and down-regulated by it. Meanwhile, TNF-α could activate NF-kB activity, which could reduce the expression of miRNA-130a [33].

**MiRNA-136:** MiRNA-136 was down-regulated in CC tissues and found as a cancer-related miRNA involved in several cancers [34], the expressions of miRNA-136 and E2F transcription factor 1 (E2F1) were correlated with locally advanced CC, middle & low differentiation, maximum lesion diameter (≥4 cm), and positive lymphatic metastasis. Moreover, miRNA-136 inhibited the proliferation of CC cells, while promoted apoptosis by targeting E2F1 through NF-kB signaling pathway [35]. Down-regulation of miRNA-136 activates Yes-Associated Protein (YAP) signaling pathway by targeting transcription factor 2 (CT2) (TFCP2) gene and promotes the proliferation, migration, and invasion of CC cells [36].

**MiRNA-143:** MiRNA-143 was down-regulated in CC and functioned as a tumor suppressor [37]. It has been proved that increased expression of miRNA-143 could inhibit the cell proliferation. Investigation revealed that over-expression of miRNA-143 markedly inhibited the proliferation and promoted apoptosis of CC cells by indirectly targeting B-cell lymphoma-2 (Bcl-2) [38]. The mechanism involves is caspase-3-mediated Bcl-2 inhibition. Moreover, the over-expressed Bcl-2 induces cell cycle arrest in S phase, whereas it interferes with the cell cycle arrest in G0/G1 phase [39]. Hypoxia-inducible factor-1α (HIF-1α) had been identified as a direct target gene of miRNA-143, over-expression of miRNA-143 could decrease the mRNA and protein levels of the former, thus inhibited the proliferation of CC cells [40].

**MiRNA-203:** MiRNA-203 was down-regulated in CC, and functioned as a tumor suppressors via directly targeting Vascular Endothelial Growth Factor Alpha (VEGF-A). The over-expression of miRNA-203 could inhibit the expression of VEGF-A both at the mRNA and protein levels, thus suppressed cell proliferation and angiogenesis [41]. MiRNA-203 was reported to target the 3’ untranslated region of barrier to auto integration factor 1 (BANF1), thus down-regulated its expression, miRNA-203 was involved in cell cycle regulation. Over-expression of miRNA-203 could suppress the cell proliferation and colony formation of CC [42], the underlying mechanism was up-regulation of miRNA-203 inhibiting the expression of survivin [43].

**MiRNA-223:** MiRNA-223 was low-expressed in CC cells, the over-expression of miRNA-223 significantly inhibited the proliferation of CC cells by targeting fork head box protein O1 (FOXO1) [44]. MiRNA-223 significantly suppressed the proliferation, growth rate, colony formation of CC cells by targeting hypoxia-inducible factor-1α (HIF-1AR) via Akt/mTOR/p70S6K pathway [45]. Abundant evidence suggested that miRNA-223 acts as a crucial regulator in CC, mainly through its targeting of related genes and interactions with various signaling pathways [16].

**MiRNA-328:** MiRNA-328 was significantly down-regulated in CC tissues and cells. The re-expression of miRNA-328 suppressed CC cell proliferation and colony formation in vitro and inhibited the growth of xenograft tumors in vivo by down-regulating the expression of transcription factor 7-like 2 (TCF7L2) [46].

**MiRNA-424-5p:** The expression of miRNA-424-5p was down-regulated in CC tissues and cells. Over-expression of miRNA-424-5p inhibited cell proliferation, but promoted cell apoptosis by directly targeting lysine specific demethylase 5B gene (KDM5B). Thus miRNA-424-5p was identified as novel anti-oncogenes by blocking cell growth through KDM5B-Notch pathway [47]. However, the function and underlying mechanisms of miRNA-424-5p in CC remains poorly elucidated.

**MiRNA-506:** The expression of miRNA-506 was down-regulated in CC samples and acted as a tumor suppressor. Recent studies showed that miRNA-506 induced cell cycle arrest at the G1/S transition, and promoted apoptosis of CC cell lines by directly targeting gli family zinc finger 3 (Gli3) [48]. In addition, fork head box Q1 (FOXO1) was validated as a new target gene of miRNA-506, the expression of miRNA-506 was inversely related to FOXQ1 expression in CC. Furthermore, the over-expression of miRNA-506 dramatically inhibited the proliferation and Epithelial-to-Mesenchymal Transition (EMT) of CC cells that mimicked the suppression of FOXO1 siRNA [49].

**Up-regulated miRNAs**

**MiRNA-2:** MiRNA-21 has been reported as an oncogenes in 6 cancer types [50], and played an important role in CC cell growth and apoptosis [51]. The inhibition of miRNA-21 in CC cells could induce profound suppression of cell proliferation by up-regulation the expression of programmed cell death 4 (PDCD4). PADC4-3’ UTR was a functional target of miRNA-21. In addition, miRNA-21 post-transcriptional down-regulates the expression of PTEN to promote cell proliferation and CC cell survival [52,53].

**MiRNA-96:** FOXO1, fork head box protein O3a (FOXO3a), reversion-inducing-cystic-inc-rich protein with kazal motifs (RECK), eph family receptor interacting proteins A5 (EphrinA5), and sterile alpha motif domain-containing 9 (SAMD9) have been identified as the targets of it in various cancers. Recently the biological function and molecular mechanism of miRNA-96 in CC was investigated. Results showed that miRNA-96 was dramatically up-regulated in CC tissues, the over-expression of miRNA-96 significantly promoted the proliferation and tumorigenicity of CC cells, which was involved silencing Protein Tyrosine Phosphatase Non-receptor type 9 (PTPN9) mechanisms [54].

**MiRNA-155:** MiRNA-155 was markedly up-regulated in CC tissues and played an oncogenic role in CC [55], which was correlated with FIGO stage, lymph nodes metastasis, vascular invasion, and HPV [56]. Down-regulation of miRNA-155 inhibited the growth of CC cells, and induced apoptosis and cell cycle arrest in G1 phase. Liver kinase B1 (LKB1) was identified as a target gene of miRNA-155, which was known as a key tumor suppressor in various cancers. The mRNA and protein expression of LKB1 was significantly reduced in CC tissues, but down-regulation the expression of miRNA-155 increased the luciferase activity and protein expression of LKB1. Thus miRNA-155 promoted the proliferation of CC cells by regulating LKB1 [57].
MiRNA-373: MiRNA-373 was up-regulated in CC tissues and cell lines and acted as an oncogenic miRNA. Ectopic over-expression of miRNA-373 promoted cell growth in vitro and tumorigenicity by directly targeting Yeast OTU Deubiquinating enzyme 1 homolog (YOD1) [58]. The underlying molecular mechanism by which miRNA-373 exerts its function in CC is still urgently needed.

Regulation of miRNA in migration, invasion, and metastasis control in CC

The metastatic cascade initiates from the detachment of a small part of cancer cells from the primary tumor, partly through morphological changes, including EMT, migration, and invasion into neighboring tissues, intravasation (transendothelial migration into blood vessels), survival in the circulation, extravasation and colonization, then secondary tumor formation. Remarkably, EMT is an essential requirement for cancer invasion and metastasis due to its making carcinoma cells dissociate from each other by losing cell-cell junctions. The transcription factors Snail, Slug, Zinc finger E-box-binding homeobox (ZEB), Twist play important roles in initiating of EMT process. The miRNA-200 family and other miRNAs have been found to regulate EMT by targeting these transcription factors. Moreover, metastasis is an important biological property of CC, and several of molecular mechanisms of miRNAs regulating the metastatic phenotypes of CC have been reported. A large amount of miRNAs widely involved in migration, invasion, and metastasis of CC have been identified and are shown in (Table 3). The complementary binding of miRNAs to the genes related to invasion and metastasis of CC silences gene expression, thus regulates the metastatic activities of CC.

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Expression status</th>
<th>Target gene</th>
<th>Related functions</th>
<th>Effect on metastasis</th>
<th>miRNA</th>
<th>Expression status</th>
<th>Target gene</th>
<th>Related functions</th>
<th>Effect on metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>miRNA-26a</td>
<td>Down</td>
<td>PRL-1</td>
<td>Cell invasion</td>
<td>Suppress invasion [59]</td>
<td>miRNA-429</td>
<td>Down</td>
<td>ZEB1/ CRKL</td>
<td>Cell migration, invasion, elongation, stress fiber formation</td>
<td></td>
</tr>
<tr>
<td>miRNA-30e</td>
<td>Down</td>
<td>GALNT7</td>
<td>Cell colony formation and invasion</td>
<td>Suppress invasion [60]</td>
<td>miRNA-433</td>
<td>Down</td>
<td>MTDH</td>
<td>Tumor size, FIGO stage, lymph node invasion, distant metastases</td>
<td></td>
</tr>
<tr>
<td>miRNA-101</td>
<td>Down</td>
<td>Cox-2</td>
<td>IFGO stage, invasion, lymph node metastasis</td>
<td>Suppress invasion [61,62, 64]</td>
<td>miRNA-454-3p</td>
<td>Down</td>
<td>C-met</td>
<td>Cell migration and invasion</td>
<td></td>
</tr>
<tr>
<td>miRNA-124</td>
<td>Down</td>
<td>AEG-1/AmotL1</td>
<td>Cell migration, invasion, EMT</td>
<td>Suppress EMT, migration, invasion [65,66]</td>
<td>miRNA-484</td>
<td>Down</td>
<td>ZEB1/SMAD2</td>
<td>Cell migration, invasion, EMT process</td>
<td></td>
</tr>
<tr>
<td>miRNA-124-3p</td>
<td>Down</td>
<td>IGF2BP</td>
<td>Cell migration and invasion</td>
<td>Suppress migration and invasion [67]</td>
<td>miRNA-485</td>
<td>Down</td>
<td>MACC1</td>
<td>Cell invasion</td>
<td></td>
</tr>
<tr>
<td>miRNA-125a-5p</td>
<td>Down</td>
<td>ABL2</td>
<td>Cell migration</td>
<td>Suppress migration and invasion [68]</td>
<td>miRNA-486-3p</td>
<td>Down</td>
<td>ECM1</td>
<td>Cell metastasis</td>
<td></td>
</tr>
<tr>
<td>miRNA-126</td>
<td>Down</td>
<td>-</td>
<td>Lymphatic invasion, distant metastasis, FIGO stage, and histological grade</td>
<td>Suppress migration and invasion [69]</td>
<td>miRNA-491-5p</td>
<td>Down</td>
<td>hTERT</td>
<td>Advanced IFGO stage, high histological grading, invasion, lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>miRNA-132</td>
<td>Down</td>
<td>SMAD2/YAP1/CCND1</td>
<td>EMT, migration, invasion</td>
<td>Suppress EMT, migration, invasion [71-73]</td>
<td>miRNA-503</td>
<td>Down</td>
<td>-</td>
<td>IFGO, and lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>miRNA-136</td>
<td>Down</td>
<td>TFCP2</td>
<td>Cell migration and invasion</td>
<td>Promote migration and invasion [36]</td>
<td>miRNA-634</td>
<td>Down</td>
<td>mTOR</td>
<td>Cell invasion</td>
<td></td>
</tr>
<tr>
<td>miRNA-138</td>
<td>Down</td>
<td>TCF3/hTERT/RMND5A</td>
<td>Advanced FIGO stage, lymph node metastasis, poor survival, EMT, migration, invasion</td>
<td>Suppress EMT, migration, invasion [74,75, 77]</td>
<td>miRNA-638</td>
<td>Down</td>
<td>-</td>
<td>Advanced FIGO stage, lymph node metastasis, vascular invasion</td>
<td></td>
</tr>
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</table>

Table 3: miRNAs involvement in cell metastasis in CC and their target genes.
<table>
<thead>
<tr>
<th>miRNA</th>
<th>Down</th>
<th>Gene</th>
<th>Function</th>
<th>miRNA</th>
<th>Down</th>
<th>Gene</th>
<th>Function</th>
<th>miRNA</th>
<th>Down</th>
<th>Gene</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>miRNA-139-3p</td>
<td>Down</td>
<td>NOB1</td>
<td>Suppress migration and invasion</td>
<td>miRNA-664</td>
<td>Down</td>
<td>E-cadherin</td>
<td>Lymphatic invasion, distant metastasis, FIGO stage, histological grade</td>
<td>Suppress migration [138,139]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>miRNA-142</td>
<td>Down</td>
<td>HMGB1</td>
<td>Suppress invasion [82]</td>
<td>miRNA-847</td>
<td>Down</td>
<td>ETS1</td>
<td>Suppress migration and invasion [140]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>miRNA-142-3p</td>
<td>Down</td>
<td>FZD7, cell invasion and metastasis</td>
<td>Suppress invasion and metastasis [81]</td>
<td>miRNA-1284</td>
<td>Down</td>
<td>HMGB1</td>
<td>Overall survival rate, invasion</td>
<td>Suppress invasion [212]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>miRNA-143</td>
<td>Down</td>
<td>GOLM1/vimentin/E-cadherin</td>
<td>Suppress migration and invasion [83,84]</td>
<td>miRNA-2861</td>
<td>Down</td>
<td>EGFRAKT2/CCND1</td>
<td>Advanced tumor stage, lymph node metastasis, invasion</td>
<td>Suppress invasion [141,142]</td>
<td></td>
<td></td>
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<tr>
<td>miRNA-144</td>
<td>Down</td>
<td>VEGFA/VEGFC</td>
<td>Suppress migration and invasion [86]</td>
<td>miRNA-let-7a</td>
<td>Down</td>
<td>PKM2/HAS2</td>
<td>Cell survival, migration, invasion, and adhesion</td>
<td>Suppress cell migration, adhesion, and invasion [143,144]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>miRNA-149</td>
<td>Down</td>
<td>GIT1</td>
<td>Suppress migration and invasion [89]</td>
<td>miRNA-10a</td>
<td>Up</td>
<td>CHL1/PTEN</td>
<td>Colony formation, lymph node metastasis, migration, invasion</td>
<td>Promote colony formation, migration, invasion [150,151]</td>
<td></td>
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<tr>
<td>miRNA-183</td>
<td>Down</td>
<td>MMP-9</td>
<td>Suppress migration and invasion [90]</td>
<td>miRNA-20a</td>
<td>Up</td>
<td>TNKS2/ATG7/TIMP2</td>
<td>Lymph node metastasis, histological grade, tumor diameter, migration, and invasion</td>
<td>Promote migration, invasion, metastasis [153,154]</td>
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<tr>
<td>miRNA-187</td>
<td>Down</td>
<td>HPV16 E6</td>
<td>Suppress migration and invasion [91]</td>
<td>miRNA-31</td>
<td>Up</td>
<td>ARID1A</td>
<td>Lymph node metastasis, vessel invasion, HPV status, metastasis</td>
<td>Promote migration and invasion [156]</td>
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<tr>
<td>miRNA-195</td>
<td>Down</td>
<td>HDGF/CCND2/MYB</td>
<td>Suppress migration and invasion [93,95]</td>
<td>miRNA-92</td>
<td>Up</td>
<td>PTEN</td>
<td>Cell migration, invasion</td>
<td>Promote migration and invasion [158]</td>
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<tr>
<td>miRNA-196b</td>
<td>Down</td>
<td>HOXB7</td>
<td>Suppress proliferation, colony formation, migration, and invasion [97]</td>
<td>miRNA-92a</td>
<td>Up</td>
<td>FBXW7</td>
<td>Cell invasion</td>
<td>Promote invasion [159]</td>
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<td></td>
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<tr>
<td>miRNA-200c</td>
<td>Down</td>
<td>MAP4K4</td>
<td>Suppress migration and invasion [99]</td>
<td>miRNA-146a</td>
<td>Up</td>
<td>-</td>
<td>Cell migration, invasion</td>
<td>Suppress migration and invasion [161]</td>
<td></td>
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<tr>
<td>miRNA-203</td>
<td>Down</td>
<td>BANF1/survivin</td>
<td>Suppress cell colony formation, migration, and invasion [102,103]</td>
<td>miRNA-146b-5p</td>
<td>Up</td>
<td>CXCR4</td>
<td>Cell invasion and adhesion</td>
<td>Suppress invasion and adhesion [163]</td>
<td></td>
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<tr>
<td>miRNA-204</td>
<td>Down</td>
<td>TCF12</td>
<td>Suppress migration and invasion [104]</td>
<td>miRNA-150</td>
<td>Up</td>
<td>PDCD4</td>
<td>Cell migration, invasion, histological grade</td>
<td>Promote migration and invasion [165,166]</td>
<td></td>
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<tr>
<td>miRNA</td>
<td>Change</td>
<td>Gene</td>
<td>Effect</td>
<td>miRNA</td>
<td>Change</td>
<td>Gene</td>
<td>Effect</td>
<td>Citation</td>
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<tr>
<td>miRNA-206</td>
<td>Down</td>
<td>Notch3</td>
<td>FIGO stage, lymph node metastasis, poor differentiation, HPV infection, migration, focus formation</td>
<td>miRNA-155</td>
<td>Up</td>
<td>-</td>
<td>Associated with FIGO stage, lymph node metastasis, vascular invasion, HPV</td>
<td>[56]</td>
<td></td>
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<tr>
<td>miRNA-211</td>
<td>Down</td>
<td>ZEB1/MUC4</td>
<td>Cell migration, invasion, EMT</td>
<td>miRNA-196a</td>
<td>Up</td>
<td>FOXO1/p27kip1/Nestin</td>
<td>Cell migration and invasion</td>
<td>[108,109]</td>
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<tr>
<td>miRNA-214</td>
<td>Down</td>
<td>ARL2/GALNT7</td>
<td>Cell migration, invasion, EMT</td>
<td>miRNA-199b-5p</td>
<td>Up</td>
<td>KLK10</td>
<td>Tumor size, FIGO stages, and preoperative metastasis</td>
<td>[111,112]</td>
<td></td>
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<tr>
<td>miRNA-320</td>
<td>Down</td>
<td>FOXM1/Mcl-1</td>
<td>Cell migration, invasion</td>
<td>miRNA-205</td>
<td>Up</td>
<td>CYR61/CTGF</td>
<td>Cell migration and invasion</td>
<td>[114,115]</td>
<td></td>
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<tr>
<td>miRNA-329-3p</td>
<td>Down</td>
<td>MAPK1</td>
<td>Histological grade, FIGO stage, lymph node metastasis, invasion, distant metastasis</td>
<td>miRNA-346</td>
<td>Up</td>
<td>AGO2</td>
<td>Cell migration and invasion</td>
<td>[116,117]</td>
<td></td>
<td></td>
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<tr>
<td>miRNA-337</td>
<td>Down</td>
<td>-</td>
<td>Tumor size, FIGO stage, lymph node metastasis, invasion</td>
<td>miRNA-361-5p</td>
<td>Up</td>
<td>-</td>
<td>Cell invasion</td>
<td>[118]</td>
<td></td>
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<tr>
<td>miRNA-338-3p</td>
<td>Down</td>
<td>MACC1</td>
<td>Advanced FIGO stage, lymph node metastasis, depth of cervical invasion, poor overall survival</td>
<td>miRNA-378</td>
<td>Up</td>
<td>ATG12</td>
<td>Tumor migration, invasion, metastasis</td>
<td>[119]</td>
<td></td>
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<tr>
<td>miRNA-342-3p</td>
<td>Down</td>
<td>FOXM1</td>
<td>Cell migration and invasion</td>
<td>miRNA-494</td>
<td>Up</td>
<td>Pttg1</td>
<td>Tumor invasion and metastasis</td>
<td>[120]</td>
<td></td>
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<tr>
<td>miRNA-362</td>
<td>Down</td>
<td>SIX1</td>
<td>Cell migration and invasion</td>
<td>miRNA-501</td>
<td>Up</td>
<td>CYLD</td>
<td>Tumor size, FIGO stage, lymph node metastasis, invasion</td>
<td>[121]</td>
<td></td>
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<td></td>
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<tr>
<td>miRNA-362-3p</td>
<td>Down</td>
<td>MCM5</td>
<td>Advanced clinical stage, poor prognosis</td>
<td>miRNA-590-5p</td>
<td>Up</td>
<td>CHL1</td>
<td>Cell invasion and colony formation</td>
<td>[122]</td>
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<tr>
<td>miRNA-375</td>
<td>Down</td>
<td>SP1</td>
<td>Lymph node metastasis, advanced clinical stage, vaginal wall extension, migration, invasion</td>
<td>miRNA-720</td>
<td>Up</td>
<td>E-cadherin/vimentin</td>
<td>EMT, cell migration</td>
<td>[123]</td>
<td></td>
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<tr>
<td>miRNA-377</td>
<td>Down</td>
<td>ZEB2</td>
<td>FIGO stage, lymph node metastasis, distant metastasis, invasion</td>
<td>miRNA-944</td>
<td>Up</td>
<td>-</td>
<td>Cell migration and invasion</td>
<td>[124]</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
**Down-regulated miRNAs**

**MiRNA-26a:** MiRNA-26a was significantly down-regulated in CC tissues and acted as a tumor suppressor in CC. The aberrant expression of miRNA-26a was a common feature of human malignancies and is correlated with poor prognosis in several cancer types. Up-regulation of miRNA-26a inhibited cell proliferation and invasion, and suppressed the growth of tumor xenografts in vivo. Protein tyrosine phosphatase type IVA 1 (PRL-1) was demonstrated as a novel target for miRNA-26a [59]. Furthermore, the expression of PRL-1 is inversely associated with that of miRNA-26a in CC tissues.

**MiRNA-30c:** As tumor suppressor, miRNA-30c was down-regulated in clinical CC tissues and cells. Over-expression of miRNA-30c reduced the CC cell growth, colony formation, and invasion. Polypeptide N-acetylgalactosaminyl transferase 7 (GALNT7) was identified as a potential target gene of miRNA-30c [60]. Both the mRNA and protein levels of GALNT7 in CC cells could down-regulated by miRNA-30c. In addition, the expression level of GALNT7 was frequently up-regulated and negatively associated with those of miRNA-30c in CC tissues.

**MiRNA-101:** MiRNA-101 was down-regulated in CC tissues and cells. It locates in 1p31.3 and has been speculated to be involved in the pathogenesis and metastasis of many cancers [61]. The expression of miRNA-101 in serum of CC patients was correlated with FIGO stage (p = 0.003), lymph node metastasis (p = 0.001), and serum squamous cell carcinoma antigen level (p = 0.007). The CC patients with a higher level of serum miRNA-101 have a longer overall survival time than that of the patients with a lower level of serum miRNA-101. Moreover, the down-regulated expression of miRNA-101 was correlated with invasion, metastasis, and unfavorable prognosis of CC [62]. MiRNA-101 arrested G1-to-S phase transition of Hela cells partially by down-regulating the expression of FOS at mRNA and protein levels [63]. Additionally, over-expression of miRNA-101 inhibited cell proliferation and invasion, induced apoptosis by decreasing the expression of its target gene cyclooxygenase-2 (Cox-2) [64]. Notably, many target genes of miRNA-101 have been found in different cancer tissues and cells, thus miRNA-101 may be correlated with a complex network of gene expression regulation.

**MiRNA-124:** MiRNA-124 was down-regulated in CC tissues and cell lines. Over-expression of miRNA-124 could dramatically suppress cell proliferation, vasculogenic mimicry, migration, invasion, and the EMT process by directly targeting astrocyte-elevated gene-1 (AEG-1) and angiomotin like 1 (AmotL1) [65,66]. Remarkably, there were a lot of studies about the function of AmotL1, including promoting the formation of vasculogenic mimicry, regulating YAP1 cytoplasmic-to-nucleus translocation, controlling endothelial migration and cell polarity, regulating sprouting angiogenesis, and controlling cell-cell adhesion. Moreover, down-regulated expression of miRNA-124-3p was found to be related to advance CC. Furthermore, miRNA-124 inhibited the growth and metastasis of CC by directly targeting insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1) [67].

**MiRNA-125-5p:** MiRNA-125a-5p was down-regulated in both CC cell lines and CC tissues, which acted as a tumor suppressor. The up-regulation of miRNA-125a-5p inhibited cell proliferation and migration of CC cells by directly targeting ABL proto-oncogene 2 (ABL2) [68]. It was found that ABL2 was significantly down-regulated at both gene and protein levels by miRNA-125a-5p up-regulation in CC cells.

**MiRNA-126:** The expression level of miRNA-126/-5p in CC tissues was markedly lower than the normal tissues. Down-regulated expression of miRNA-126 in CC was significantly correlated with lymphatic invasion (p = 0.002), distant metastasis (p < 0.001), FIGO stage (p = 0.009), and histological grade (p = 0.005). These results displayed that miRNA-126 might be a marker of prognosis for patients with CC [69]. In addition, over-expression of miRNA-126-5p promoted cell apoptosis of CC cells by directly targeting Bcl212, the level of the latter was significantly down-regulated by miRNA-126-5p [70].

**MiRNA-132:** MiRNA-132 was aberrantly down-regulated in CC tissues. Over-expression of miRNA-132 not only inhibited G1/S phase transition and cell proliferation, but also suppressed EMT, migration, and invasion in CC cells by targeting drosophila mothers against decapentaplegic protein 2 (SMAD2) [71]. In addition, over-expression of miRNA-132 down-regulated the levels of proliferation-associated molecules marker of proliferation Ki-67 and proliferating cell nuclear antigen, and inhibited the production of MMP-2 and MMP-9 [72]. Moreover, YAP1 and cyclin D1 (CCND1) were identified as another two target genes [73].

**MiRNA-138:** MiRNA-138 was down-regulated in both CC tissues and CC cells; low expression of it in CC was closely related to advanced FIGO stage, lymph node metastasis, and poor survival. Up-regulation of miRNA-138 inhibited cell proliferation, migration, and invasion in vitro, and xenograft growth in vivo by directly targeting transcriptional factor 3 (TCF3) and Human Telomerase Reverse Transcriptase (HTERT) [74,75]. Earlier research demonstrated that the miRNA-138 inhibited CC cells proliferation via C-met [76]. In addition, miRNA-138 could significantly suppress HeLa cell migration through targeting required for meiotic nuclear division 5 homolog A (RMND5A) [77]. MiRNA-138 inhibited HeLa cell migration, possibly through a complex multistep process, which involved in the inhibition of RMND5A protein function and regulation of general miRNA expression. Furthermore, common phenomenon in other cancer cells was found.

**MiRNA-139-3p:** MiRNA-139-3p was reported to be down-regulated in CC tissues and cell lines, and acted as a tumor suppressor. Over-expression of miRNA-139-3p significantly inhibited cell proliferation, migration, and invasion but promoted cell apoptosis N11/RPN12 binding protein 1 homolog (NOB1) has been identified as its targeting gene [78]. Over-expression of NOB1 counteracted the effects of miRNA-139-3p suppression. Moreover, NOB1 was highly expressed in several cancer types and played an important role in universal biological processes. Over-expression of miRNA-139-3p significantly inhibited both the expression of NOB1 and the luciferase reporter activity of NOB1 3'-UTR.

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Down-regulated</th>
<th>Tumor size, FIGO stage, lymph node metastasis, invasion, distant metastasis</th>
<th>Suppress invasion [125]</th>
</tr>
</thead>
<tbody>
<tr>
<td>miRNA-411</td>
<td>Down</td>
<td>STAT3</td>
<td></td>
</tr>
</tbody>
</table>

| miRNA-124 | MiRNA-124 was down-regulated in CC tissues and cell lines. Over-expression of miRNA-124 could dramatically suppress cell proliferation, vasculogenic mimicry, migration, invasion, and the EMT process by directly targeting astrocyte-elevated gene-1 (AEG-1) and angiometin like 1 (AmotL1) [65,66]. Remarkably, there were a lot of studies about the function of AmotL1, including promoting the formation of vasculogenic mimicry, regulating YAP1 cytoplasmic-to-nucleus translocation, controlling endothelial migration and cell polarity, regulating sprouting angiogenesis, and controlling cell-cell adhesion. Moreover, down-regulated expression of miRNA-124-3p was found to be related to advance CC. Furthermore, miRNA-124 inhibited the growth and metastasis of CC by directly targeting insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1) [67]. |
| MiRNA-125-5p | MiRNA-125a-5p was down-regulated in both CC cell lines and CC tissues, which acted as a tumor suppressor. The up-regulation of miRNA-125a-5p inhibited cell proliferation and migration of CC cells by directly targeting ABL proto-oncogene 2 (ABL2) [68]. It was found that ABL2 was significantly down-regulated at both gene and protein levels by miRNA-125a-5p up-regulation in CC cells. |

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MiRNA-142: MiRNA-142 and miRNA-142-3p was down-regulated in CC tissues and cell lines. Low miRNA-142-3p expression level was significantly associated with advanced FIGO stage, lymph node metastasis, and depth of cervical invasion [79]. In addition, over-expression of miRNA-142-3p inhibited proliferation and invasion of CC cells by down-regulating Frizzled 7 receptor (FZD7) [80]. Moreover, High-Mobility Group AT-hook 2 (HMGA2) and High-Mobility Group Box1 protein (HMGBI1) was another two targets of miRNA-142-3p and miRNA-142 [81,82]. Recent studies have reported that miRNA-142 and HMGB1 is associated with the progression of tumors by binding to their target genes. It was identified that miRNA-142 targeted at HMGBI1 and inhibited their expression at translation level in CC cells.

MiRNA-143: MiRNA expression was dramatically down-regulated in both CC tissues and cells. The expression of miRNA-143 was negatively associated with the Golgi Membrane Protein 1 (GOLM1) expression. Over-expression of miRNA-143 significantly inhibited SiHa and HeLa cell migration and invasion by directly suppressing the expression of GOLM1 [83]. In addition, low expression of miRNA-143 could enhance the expression of vimentin, but reduce the expression of E-cadherin, thus potentiate proliferation of the CC cell line Hela, and promote its migration and invasion [84].

MiRNA-144: The inhibition of more than 19 miRNAs, including miRNA-144, 95, 124, 12S, 133, and 134, caused a decrease in cell growth of CC cells [85]. Remarkably, recent studies confirmed that miRNA-144 located on chromosome 17q11.2 of human genome and negatively regulated the metastasis of CC. Moreover, miRNA-144-3p was found to be a novel direct target of miRNA-144 and negatively regulated by it. The mechanism involved was PI3K/AKT/mTOR pathway, which was negatively regulated by miRNA-149 [85].

MiRNA-145: MiRNA-145 expression was significantly down-regulated in CC tissues and cell lines. The expression of miRNA-145 was associated with advanced cancer stages, large tumor size, and moderate/poor differentiation [87]. In addition, miRNA-145 over-expression prohibited tumor invasion and colony formation of CC cells [88].

MiRNA-146: MiRNA-149 was a tumor suppressor and down-regulated both in CC tissues and cell lines. The restoration of miRNA-149 expression inhibited cell proliferation, migration, invasion, and promoted cell apoptosis in vitro. In addition, over-expression of miRNA-149 suppressed the growth of CC cells in vivo. Recent studies indicate that G-Protein-Coupled Receptor (GPCR)-kinase interacting protein-1 (GIT1) interacts with G-Protein-Coupled Receptor (GPRC) and suppresses its activity, resulting in reduced migration and invasion of CC cells. GIT1 was identified as a novel direct target of miRNA-149 and negatively regulated by it. The mechanism involved was PI3K/AKT/mTOR pathway, which was negatively regulated by miRNA-149 [89].

MiRNA-187: The miRNA-187 expression levels were dramatically down-regulated in CC tissues; Ectopic expression of miRNA-187 could suppress the migration and invasion of CC cell lines by remarkably up-regulating MMP-9 in CC [90]. It was reported that MMP-9 was involved in the invasion and metastasis of CC, as well as other malignant tumors.

MiRNA-195: MiRNA-195 was down-regulated in CC tissues and cell lines. Up-regulation of miRNA-195 and knockdown of Hepatoma-Derived Growth Factor (HDGF) suppressed cell proliferation, migration, and invasion of CC cells. It was identified that miRNA-195 inhibited the behavior of tumors in CC by targeting HDGF [93]. Moreover, over-expression of miRNA-195 induced G1 phase arrest by directly targeting cyclin D1a (CCND1a) mRNA. As the key cell cycle regulators, the levels of p-Rb and PCNA were significantly down-regulated by miRNA-195, thus prolonged G1 phase in the CC cells [94]. In addition, miRNA-195 suppressed cell proliferation, migration, and invasion by repressing the expression of cyclin D2 (CCND2) and V-MYB avian myeloblastosis viral oncogenes homolog (MYB) in CC cells at the mRNA and protein levels [95].

MiRNA-196b: The expression of miRNA-196a was dramatically down-regulated in both CC tissues and cells. The CC patients with low expression of miRNA-196b experienced worse disease-free survival than those with high miRNA-196b expression. Homeobox-B7 (HOXB7) was verified as a direct and specific target of miRNA-196b [96], VEGF was demonstrated as a downstream transcriptional target of HOXB7 in CC. Pre-miRNA-196b transfection decreased cell viability, clonogenicity, migration, and invasion [97]. Furthermore, forced expression of miRNA-196b significantly inhibited apoptosis, but enhanced the viability of Hela cells [98]. The miRNA-196b/HOXB7/VEGF pathway was demonstrated to play an important role in CC progression. Thus targeting miRNA-196b/HOXB7/VEGF pathway may be a potential therapeutic strategy for the treatment of CC.

MiRNA-200c: MiRNA-200c was significantly down-regulated in CC tissues and cell lines. Over-expression of miRNA-200c in CC cells dramatically suppressed cell proliferation, migration, and invasion. Mitogen-activated protein kinase 4 (MAP4K4) was confirmed as a target gene of miRNA-200c [99]. Studies indicated that MAP4K4 is over-expressed in many cancer cells, which is involving in accelerating cell transformation, promoting cell invasion, but reducing the adhesion to tissue culture cells, and affecting the prognosis of cancer. The expression of MAP4K4 was displayed to be negatively associated with miRNA-200c in CC tissues and cells. In addition, miRNA-200a can regulate the metastasis of CC and be used to predict the survival of patients, and miRNA-200b is lowly expressed in the invasive CC and inhibits the invasion and metastasis of CC via suppressing the EMT of CC.

MiRNA-202: The expression of miRNA-202 was significantly down-regulated in both CC tissues and cell lines, it expression was negatively correlated with the expression of CCN1 [100]. Over-expression of miRNA-202 suppressed the expression of CCN1 protein by targeting its 3’-UTR of the latter. The ectopic expression of miRNA-202 inhibited the cell proliferation, migration, and invasion of both SiHa and HeLa cells. However, over-expression of CCN1 reversed the inhibitory effects of over-expressed miRNA-202 on CC cell proliferation, migration, and invasion. Thus, miRNA-202 may be an effective tumor-suppressing miRNA for the treatment of CC patients.
MiRNA-203: MiRNA-203 was frequently down-regulated in CC tissues and cell lines. It was found that miRNA-203 down-regulated the expression of VEGFA by directly targeting it 3'-UTR [101]. The miRNA-203 levels were negatively associated with VEGFA levels. Furthermore, miRNA-203 suppressed CC cell proliferation, tumor growth, and angiogenesis in vivo. In addition, over-expression of miRNA-203 suppressed cell proliferation and migration, and down-regulated the expression of survivin. Whereas, down-regulation of miRNA-203 expression had no effect on the proliferation, migration, or survivin expression in CC cells [102]. Furthermore, miRNA-203 was indicated to regulate cell cycle of CC, and over-expression of miRNA-203 suppressed cell colony formation and invasion of CC cells partially by down-regulating its target, BANF1 [103].

MiRNA-204: MiRNA-204 was significantly decreased in CC tissues and acted as a tumor suppressor; the down-regulated miRNA-204 was associated with lymph node metastasis and poor survival. It was revealed that ectopic expression of miRNA-204 dramatically suppressed the migration and invasion of CC cells by directly targeting transcription factor 12 (TCF12) [104]. Furthermore, miRNA-204 was demonstrated to act as a metastasis-associated gene in CC.

MiRNA-205: The expression of miRNA-205 in CC tissues is significantly down-regulated and acts as a diagnostic and prognostic marker. Lower level of miRNA-205 was associated with FIGO stage, lymph node metastasis, poor differentiation, and HPV infection. In addition, over-expression of miRNA-206 could suppress cell proliferation, induce cell apoptosis, and inhibit cell invasion and migration [105]. Moreover, miRNA-206 suppressed cell proliferation by directly targeting the Glucose-6-Phosphate Dehydrogenase (G6PD) [106]. In addition, over-expression of miRNA-206 dramatically promoted cell apoptosis, but inhibited cell migration and focus formation by targeting Notch3 [107].

MiRNA-206: MiRNA-211 acted as a tumor suppressor in CC, the expression level of miRNA-211 in CC tissues and cell lines was significantly lower than normal ones. Up-regulation of miRNA-211 could suppress cell proliferation, migration, and invasion of CC. Zinc finger E-box binding homeobox 1 (ZEB1) was identified as a direct target gene of miRNA-211. The expression of ZEB1 at mRNA and protein levels was markedly reduced by the over-expression of miRNA-211 [108]. Moreover, miRNA-211 could suppress CC cell invasion and EMT by down-regulating the expression of mucin 4 (MUC4) [109]. MUC4, as a member of Mucins family, which is up-regulated in several cancers, involving EMT, cell migration, invasion, and metastasis.

MiRNA-207: MiRNA-214, as a suppressor gene, which was down-regulated in CC tissues and associated with tumor differentiation and tumor stage. Over-expression of miRNA-214 reduced the proliferation of CC cells by directly targeting Enhancer of Zeste Homolog 2 (EZH2) [110]. In addition, over-expression of miRNA-214 suppressed proliferation, migration, and invasion of CC cell lines through targeting ADP ribosylation factor like 2 (ARL2) [111] and GALNT7 [112]. Moreover, ectopic expression of miRNA-214 reduced cell survival, but induced apoptosis of CC cells through directly suppressing Bcl212 expression in CC cells. The apoptosis induced by miRNA-214 was correlated with up-regulation expression of Bax, caspase-3, -8, and -9 [113].

MiRNA-208: MiRNA-320 was markedly down-regulated in CC tissues and cell lines. Over-expression of miRNA-320 repressed the viability, migration, and invasion of CC cells. MiRNA-320 negatively regulated the expression of fork head box M1 (FOXM1) and acted as a tumor suppressor [114]. In addition, miRNA-320 was found to induce cell apoptosis via down-regulation of myeloid cell leukemia-1 (Mcl-1) and activation of caspase-3, but suppress cell proliferation, migration, invasion, and tumorigenesis in CC cells [115].

MiRNA-329-3p: The expression levels of miRNA-329-3p were down-regulated in both CC tissues and cell lines and acted as a tumor suppressor. Low miRNA-329-3p expression was negatively associated with histological grade, FIGO stage, lymph node metastasis, and distant metastasis of CC patients. Mitogen-Activated Protein Kinase 1 (MAPK1) was demonstrated to be significantly up-regulated and negatively correlated with miRNA-329-3p expression in the CC tissues. Inhibition of MAPK1 by RNA interference suppressed cell proliferation, invasion, metastasis, but promoted apoptosis of CC. Moreover, up-regulation of miRNA-329-3p inhibited cell proliferation, migration, and invasion of CC by directly targeting MAPK1 [116,117]. Therefore, MAPK1 may be a potential therapeutic target for the treatment of CC patients.

MiRNA-337: MiRNA-337 expression was significantly down-regulated both in CC tissues and cell lines. The aberrant expression of miRNA-337 was positively associated with tumor size, FIGO stage, and lymph node metastasis of CC. The ectopic expression of miRNA-337 inhibited cell proliferation and invasion by directly targeting Specificity Protein 1 (SP1) [118]. Furthermore, the expression of SP1 was up-regulated in CC tissues and negatively associated with the expression level of miRNA-337. SP1 expression was reported to be up-regulated in several cancers, and to be correlated with cell growth, differentiation, migration, metastasis, and invasion of multiple tumors. In addition, SP1 is involved in cell proliferation, apoptosis, radio-sensitivity, and metastasis of CC.

MiRNA-338-3p: The expression of miRNA-338-3p was shown substantially down-regulated in CC tissues and corrected with advanced FIGO stage, lymph node metastasis, depth of cervical invasion, and poor overall survival. Metastasis-Associated in Colon Cancer-1 (MACC1) was identified as a functional downstream target for miRNA-338-3p. Both of them had been proven to be involved in the progression of CC cells by regulation MAPK signaling pathway [119]. Moreover, MACC1 was reported to be up-regulated in CC tissues and negatively regulated by miRNA-338-3p at the miRNA and protein expression level. Recent studies showed that MACC1 played important roles in CC progression, such as poor prognosis, invasion, and angiogenesis.

MiRNA-342-3p: MiRNA-342-3p was down-regulated in CC tissues. FOXM1, as an oncogenic factor, has been reported to participate in multiple biological processes, such as cell proliferation, angiogenesis, migration, and invasion. Furthermore, FOXM1 was found to be up-regulated and negatively correlated with miRNA-342-3p in CC tissues. The over-expression of the latter suppressed cell growth, migration and invasion of CC cell lines is directly targeting FOXM1 [120].

MiRNA-362: The expression level of miRNA-362 was significantly lower in CC tissues and cell lines than the normal ones, which could repress cell proliferation, migration, and invasion in CC through its targeting gene sine oculis homeobox homolog 1 (SIX1) [121]. In addition, miRNA-362-3p was also down-regulated in CC tissues and cell lines, and negatively regulated mini chromosome maintenance protein 5 (MCM5) mRNA and protein expression through directly targeting its 3'UTR. MCM5 high expression was found to be
correlated with lymph node metastasis, present distant metastasis, and low histological grade of CC. Thus low-expression was related to advanced clinical stage and poor prognosis [122].

MiRNA-375: The expression of miRNA-375 was significantly down-regulated in CC tissues. There was a significant correlation between miRNA-375 expression and clinicopathological parameters, such as lymph node metastasis of CC. Low-expression of miRNA-375 was closely associated with lymph node metastasis, advanced clinical stage, and vaginal wall extension. Over-expressed miRNA-375 inhibited cell proliferation, arrested G1-to-S cell-cycle transition, as well as suppressed both cell migration and invasion in CC cells. SP1 was identified as a potential target gene of miRNA-375 [123].

MiRNA-377: MiRNA-377 was down-regulated in CC tissues and cell lines. Down-regulation of miRNA-377 was significantly associated with FIGO stage, lymph node metastasis, and distant metastasis in CC patients. Up-regulation of miRNA-377 inhibited cell proliferation and invasion in CC by directly targeting ZEB2 [124]. Moreover, ZEB2 was confirmed to be over-expressed in CC tissues and was negatively associated with the miRNA-377 level.

MiRNA-411: MiRNA-411 was significantly down-regulated in both CC tissues and cell lines; the down-regulation of miRNA-411 was associated with tumor size, FIGO stage, lymph node metastasis, and distant metastasis. In addition, the over-expression of miRNA-411 inhibited cell proliferation and invasion in CC. Signal transducer and activator of transcription 3 (STAT3) was identified as a direct target of miRNA-411 [125]. The expression levels of miRNA-411 were inversely associated with STAT3, which was significantly over-expressed in CC.

MiRNA-429: MiRNA-429 was down-regulated in CC tissues, which was suggested as a member of the miRNA-200 family. Recent studies indicated that miRNA-429 inhibited cell viability and proliferation while promoting apoptosis in CC cells [126]. IkappaB kinase beta (IKKβ) was identified as a novel target gene of miRNA-429 in NF-κB pathway. In addition, miRNA-429 modulated cell migration, invasion, elongation, as well as stress fiber formation induced by TGF-β through regulation of its targeting genes ZEB1 and CRKL [127]. It was found that miRNA-429 played an inhibited role in ZEB1 and CRKL expression, thus suppressed the tumor progression, both ZEB1 and CRKL could inhibit neural precursor cell-expressed developmentally down-regulated gene 4-like (NEDD4L) while promote SMAD2/3 expression, thus inhibiting apoptosis progression.

MiRNA-433: MiRNA-433 was significantly down-regulated in CC tissues and cell lines. Low miRNA-433 expression was confirmed to markedly correlate with tumor size, FIGO stage, lymph node, and distant metastases. MiRNA-433 inhibited cell proliferation, invasion, and induced apoptosis in CC cells by directly targeting metadherin (MTDH) via the AKT and β-catenin signaling pathways [128]. In addition, down-regulation of miRNA-433 promoted the proliferation, and suppressed the apoptosis of CC cells through activating FAK/AKT signaling pathway [129].

MiRNA-454-3p: MiRNA-454-3p was down-regulated in CC cell lines. Over-expression of miRNA-454-3p dramatically suppresses cell proliferation, migration, and invasion. C-met was identified as a novel target of miRNA-454-3p [130]. C-met was up-regulated in various cancer types and a significant prognostic value in early-stage invasive and local-regional advanced CC patients. It is believed that miRNA-454-3p suppresses cell proliferation, migration, and invasion partly due to targeting C-met, thus down-regulates the protein levels of downstream effectors of the latter, including p-Akt, MMP-2, and MMP-9.

MiRNA-484: MiRNA-484 was down-regulated in CC tissues and cell lines. It was reported that ZEB1 played an important role in the progression and metastasis in many cancer types, and SMAD2 could promote cell proliferation by facilitating the G1/S phase transition. Over-expression of miRNA-484 inhibited cell proliferation, while promoted apoptosis. Besides, miRNA-484 suppressed migration, invasion, and EMT process of CC cells. Both ZEB1 and SMAD2 were demonstrated as the targeting gene of miRNA-484, the expression levels of them were negatively correlated with that of miRNA-484 [131].

MiRNA-485: MiRNA-485 expression was dramatically down-regulated in CC tissues and cell lines. Down-expression of miRNA-485 in CC patients was associated with IFGO and lymph node metastasis. Furthermore, restored expression of miRNA-485 dramatically inhibited cell proliferation and invasion of CC cells [132]. MACC1 was verified as a direct target gene of miRNA-485 and inversely associated with it expression. Notably, restored expression of MACC1 could eliminate the suppressive effects of miRNA-485 over-expression on the proliferation and invasion of CC cells. These results confirmed that miRNA-485 may play its tumor suppressive effect on CC by directly targeting MACC1 and inhibiting the Met/AKT signaling pathway. Thus, the miRNA-485/MACC1 axis may be a novel and effective therapeutic target in CC.

MiRNA-486-3p: The expression of miRNA-486-3p was down-regulated in CC tissues and acted as a suppressor in CC. Clinical data demonstrated that down-regulated miRNA-486-3p was correlated to metastasis in CC patients. In addition, Extra Cellular Matrix protein 1 (ECM1) was verified as a target gene of miRNA-486-3p, which is associated with poor clinical prognosis and metastasis in cancer [133]. Over-expression of miRNA-486-3p suppressed cell growth and metastasis of CC by down-regulating the expression of ECM1.

MiRNA-491-5p: The expression of miRNA-491-5p was significantly down-regulated in CC tissues and negatively associated with advanced FIGO stage, high histological grading, and lymph node metastasis. The up-regulated expression of miRNA-491-5p in CC cells dramatically suppressed proliferation, migration, and invasion, induced cell apoptosis by targeting hTERT via PI3K/AKT signaling pathway [134]. Accumulating evidence has shown that hTERT play a vital role in cancer tumorigenesis, growth, migration, and invasion. In addition, down-regulation of hTERT suppressed the PI3K/AKT signaling pathway.

MiRNA-503: MiRNA-503 expression was significantly down-regulated in CC tissues. The expression of miRNA-503 in CC patients was significantly associated with recurrence, FIGO stage, and lymph node metastasis of CC. Additionally, miRNA-503 expression was confirmed as an independent prognostic factor for both CC recurrence-free and overall survival [135]. Low expression of miRNA-503 associated with high recurrence rate of CC, thus it may be used as a potential biomarker to predict the risk of recurrence in CC patients.

MiRNA-634: MiRNA-634 was down-regulated in CC tissues and acted as an antioncogene. Compelling research confirmed that miRNA-634 was not only associated with cell proliferation but also related to the invasion of CC cells through regulating the expression of mammalian target of rapamycin (mTOR) [136]. The results indicated
that down-expression of miRNA-634 enhanced the mTOR expression at both the mRNA and protein levels.

**MiRNA-638:** The expression of miRNA-638 in CC tissues and cell lines was down-regulated and located in the 19p13.2 region. Low expression of miRNA-638 was significantly associated with advanced FIGO stage, lymph node metastasis, and vascular invasion. In addition, over expression of miRNA-638 suppressed cell migration and invasion through inhibiting the activation of Wnt/β-catenin signaling pathway [137].

**MiRNA-664:** MiRNA-664 was down-regulated in both CC tissues and cell lines. Recent results revealed that miRNA-664 was associated with prognosis of CC. Low miRNA-664 expression was significantly related to lymphatic invasion, distant metastasis, FIGO stage, and histological grade [138]. Previous studies had confirmed that both the mRNA and protein levels of E-cadherin were down-regulated in metastatic carcinomas of CC. E-cadherin was a direct target site of miRNA-200 family in regulation of EMT in various cancer types. Up-regulation of miRNA-664 suppressed cell migration of CC, which was possibly modulated by significantly up-regulating the protein expression of E-cadherin [139].

**MiRNA-847:** MiRNA-847 was frequently dysregulated in various types of human cancer and down-regulated in CC tissues and cells, and its down-regulation was associated with IFGO stage and lymph node metastasis. The up-regulation of miRNA-847 suppressed the proliferation, migration, and invasion, but promoted the apoptosis of CC cells by directly inhibiting E26 transformation specific-1 (ETS1) [140]. Furthermore, the expression of ETS1 was reported to be up-regulated in CC tissues, and the over-expression of ETS1 was inversely correlated with that of miRNA-874. It was noteworthy that reintroduction of ETS1 expression counteracted the inhibiting effects of miRNA-874 overexpression in CC cells.

**MiRNA-2861:** MiRNA-2861 was found down-regulated in CC tissues and sera of CC patients, and negatively related to advanced tumor stage and lymph node metastasis [141]. Over-expression of miRNA-2861 inhibited the proliferation and invasion, but enhanced the apoptosis of CC cells. EGFR, AKT2, and CCND1 were identified as the direct targets of miRNA-2861 [142]. It was demonstrated that over-expression of miRNA-2861 suppressed the EGFR/AKT2/CCND1 pathway in CC cells.

**MiRNA-let-7a:** The miRNA-let-7 family members have been extensively studied and identified as tumor suppressor miRNAs, due to their down-expression in various cancers. The current understanding suggests that miRNA-let-7 could induce cell apoptosis, and play a vital role in drug resistance of cancer cells. Previous studies identified that miRNA-let-7a was down-regulated in CC tissues and cell lines. Low miRNA-let-7a expression in CC was significantly associated with advanced FIGO stage, lymph node metastasis, and tumor size. Over-expression of miRNA-let-7a inhibited SiHa and HeLa cell proliferation, migration, invasion, and promoted cell apoptosis. Furthermore, miRNA-let-7a was inversely correlated with Pyruvate Kinase Muscle isozyme M2 (PKM2) at both mRNA and protein levels (p=0.013 and p=0.015, respectively) [143]. Additionally, inhibiting the expression of miRNA-let-7 by ectopic expression of the anti-miRNA-let-7 increased the cell survival, invasion, and adhesion of HeLa cells. Hylauronian Synthase 2 (HAS2) was identified as a novel target for miRNA-let-7, which could be suppressed by the latter [144]. Furthermore, ubiquitin specific protease 35 (USP35) may be another target of miRNA-let-7 [145].

**Up-regulated miRNAs**

**MiRNA-9:** MiRNA-9 was significantly over-expressed in CC tissue and cells, which could be specifically activated by HPV in a p53-independent manner. Both activation of miRNA-9 and suppression of its targets could enhance mobility of HPV hosting cells, which eventually resulted in metastatic cancer [146]. Moreover, it was found that over-expression of miRNA-9 promoted cell proliferation, cell cycle transformation, but suppressed apoptosis of CC cells by suppressing PDCD4 expression in CC cells, and it could also promote HeLa cell turning into G2 phase from S phase [147]. Recent studies indicated that miRNA-9 could promote the proliferation and migration of CC cells in vitro and in vivo. Down-regulation of miRNA-9 increased the expression of FOXO3, and regulated FOXO3 downstream proteins Bax, Bcl-2, and p-Akt expressions [148]. Furthermore, miRNA-9 promoted the migration and invasion of CC cells by directly targeting FOXO1, and over-expression of miRNA-9 suppressed the expression level of FOXO1 [149].

**MiRNA-10a:** MiRNA-10a was up-regulated in CC and promoted the colony formation activity, migration, and invasion of CC cells. Close homologue of L1 (CHL1) was identified as a target of miRNA-10a and was negatively regulated by it [150]. Notably, previous studies have indicated that CHL1 is frequently over-expressed in most cancers, but recent study showed that it is poorly expressed in CC tissues. In addition, miRNA-10a was demonstrated to be markedly up-regulated in primary tumor tissues in CC patients with positive lymph node metastasis, and significantly promote CC cell migration and invasion by targeting PTEN [151]. However, as a member of miRNA-10 family, miRNA-10a-5p was demonstrated to be significantly down-regulated in CC cells. Over-expression of miRNA-10a-5p markedly suppressed cancer cell viability, and induced cell cycle arrest by reducing Brain-derived Neurontrophic Factor (BDNF) gene expression [152].

**MiRNA-20a:** As an important member of the miRNA-17–92 cluster, miRNA-20a was demonstrated up-regulated in CC tissues. Over-expression of miRNA-20a promoted cellular proliferation, migration, and invasion, but down-regulation of miRNA-20a inhibited those functions. Oncogenic tankyrase 2 (TNKS2) is responsible for the protection of the ends of linear chromosomes, and identified as an auto-antigen in various cancer patients, which has been confirmed directly up-regulated by miRNA-20a [153]. In addition, the aberrant expression of miRNA-20a was related to lymph node metastasis, histological grade, and tumor diameter. CyclinB1, CCND1, and CDK2 are pivotal for the driving transition from G2 phase to M phase and G1 phase to S phase, respectively. The results indicated that over-expression of miRNA-20a significantly increased expression of CyclinB1, CCND1, and CDK2 at both mRNA and protein levels, thus promoted cell growth in CC. Down-regulation of miRNA-20a suppressed tumor progression by modulation cell cycle, apoptosis, and metastasis in vitro and in vivo. Furthermore, tissue inhibitor of metalloproteinase’s 2 (TIMP2), autophagy-related protein 7 (ATG7), and PDCD6 was confirmed to be direct targets of miRNA-20a [154,155]. Notably, ATG7 is one of the master regulators of the autophagy process; TIMPs could regulate the activities of MMPs to control the degradation of basement membranes and remodeling the extracellular matrix, thus regulate the process of tumor invasion.

**MiRNA-31:** The expression level of miRNA-31 was significantly high, locates on the 9p21.3 chromosome, and acted as an oncogene in CC. A aberrant expression of miRNA-31 was correlated with the lymph node metastasis, vessel invasion, and HPV status. Over-expression of
miRNA-31 could promote cell proliferation, migration, and invasion of CC cells [156]. In addition, the high expression of miRNA-31 was significantly associated with higher FIGO stage, node metastasis, vascular involvement, and deep stromal invasion. Patients with high expression of miRNA-31 had poor overall survival. It was reported that miRNA-31 promoted CC cell growth both in vitro and in vivo by suppressing apoptosis, as well as enhancing migration and invasion in vitro. Down-expression of miRNA-31 inhibited cell proliferation, colony formation, migration, and invasion in vitro and suppressed xenograft tumor growth in vivo. AT-rich interactive domain 1A (ARID1A), as a member of SWI/SNF chromatin remodeling complexes, is involved in the initiation and development of cancers by suppressing cell proliferation, and promoting invasion and metastasis. MiRNA-31 was demonstrated to enhance growth and invasion of CC by inhibiting the expression of ARID1A [157].

MiRNA-92: MiRNA-92 and miRNA-92a was up-regulated in the CC tissues and cell lines. In the HPV16-positive CC tissues, the expression of miRNA-92 was higher than the HPV16-negative ones. MiRNA-92 dramatically promoted cell proliferation, migration and invasion, but suppressed apoptosis of CC cells partially through down-regulating the expression of PTEN [158]. In addition, over-expression of miRNA-92a was significantly correlated with lymph node metastasis and advanced clinical stage in CC, and remarkably enhanced proliferation by promoting cell cycle transition from G1 to S phase, and significantly promoting invasion of CC cells by targeting F-box and WD repeat domain-containing 7 (FBXW7). FBXW7 acts as a potential tumor suppressor, which is frequently mutated and deleted in several of human tumors. The expression level of FBXW7 mRNA was suppressed by miRNA-92a via direct binding to its 3'-UTR [159]. Down-regulation of miRNA-92a inhibited the proliferation of HeLa cells by arresting cell cycle at the G1 stage by targeting p21. It was confirmed that miRNA-92a has a negative effect on protein levels of p21 in HeLa cells [160].

MiRNA-146: MiRNA-146a was up-regulated in CC tissues and cell lines; however, ectopic expression of miRNA-146a suppressed proliferation of CC cells, and inhibited their migration and invasion [161,162]. Moreover, miRNA-146b was demonstrated to inhibit the proliferation, invasion, and adhesion of CC cells, as well as block the cell cycle progression by targeting C-X-C chemokine receptor-4 (CXCR4) [163]. Moreover, it was hypothesized that miRNA-146b-5p was not only associated with the down-regulation of MMP-2, MMP-9, cancer myelocytomatosis oncogene (c-Myc), CCND1, and telomerase activity, but also related to the up-regulation of p27 and p53, the down-regulation of TGF-β, TNF-α, and other cytokine secretions.

MiRNA-150: The expression of miRNA-150 in CC was significantly up-regulated and acted as an oncogene. Recent studies demonstrated that miRNA-150 promoted CC cell survival and growth. MiRNA-150 also promoted the cell cycle progression from G1/G0 to S phase and modulated several cell cycle- and apoptosis-related genes, including CCND1, p27, BIM, and Fasl. In addition, miRNA-150 directly down-regulated the expression is FOXO4, which regulated the expression of the above genes by targeting its 3' UTR [164]. Furthermore, miRNA-150 was confirmed to promote cell migration and invasion of CC cells through targeting PDCD4 [165]. Over-expression of miRNA-150 is remarkably correlated with worse histological grade, lymph node metastasis, and lymphatic invasion [166].

MiRNA-196a: The expression of miRNA-196a was dramatically up-regulated in both CC tissues and cells. The over-expression of miRNA-196a was associated with advanced tumor stage and poor overall and recurrence-free survival in CC patients. Over-expression of miRNA-196a promoted G1/S-phase transition and proliferation of CC cells [167]. As two vital effectors of PI3K/AKT signaling, FOXO1 and p27kip1, were identified as the direct targets of miRNA-196a, which could be inhibited by the latter. In addition, over-expression of miRNA-196a could promote cell proliferation and migration of CC cells [168]. Netrin 4 was found to be negatively associated with miRNA-196a. Recent evidence has shown that miRNA-196a is involved in multiple biological processes, including cell proliferation, migration, and invasion, which may serve as a novel biomarker or target for diagnosis, prognosis, and therapy in CC [169]. All these studies indicate that suppression the expression of miRNA-196a may be a novel therapeutic strategy in the treatment of CC.

MiRNA-199: MiRNA-199b-5p was up-regulated in CC tissues and cell lines. It was positively associated with overall survival, progression-free survival, and higher incidences of larger tumor size, late FIGO stages, and preoperative metastasis. Moreover, miRNA-199b-5p was found to play as a tumor promoter in CC cell growth by targeting kallikrein-related peptidase 10 (KLK10) [170]. The latter has been identified as a tumor suppressor gene, which can suppress cell proliferation, glucose metabolism, but promote apoptosis of multiple cancer cells. It was indicated that miRNA-199b-5p enhanced the cell viability, migration, but suppressed apoptosis by directly down-regulating KLK10 via targeting the 3'-UTR of the gene. Furthermore, miRNA-199b-5p over-expression regulated the migration of CC cells accompanied with down-expressed E-cadherin, but up-expressed N-cadherin, vimentin, and MMP-2, which indicated that miRNA-199b-5p regulated the CC metastasis through mediating EMT and MMP members expressions.

MiRNA-205: MiRNA-205 was identified as an oncogene, which was up-regulated in tissues and serum of CC patients, and could modulate the expression of multiple cancer-related target genes [171]. Notably, patients with high serum miRNA-205 levels had a remarkably lower survival rate than those with low expression levels. The high level of miRNA-205 expression was associated with poor tumor differentiation (p=0.009), lymph node metastasis (p=0.015), and increased tumor stage (p=0.001). The miRNA-205 was demonstrated to promote cell proliferation and migration of CC cells. Cystein-rich61CTGF, (CYR61) and Connective Tissue Growth Factor (CTGF) were identified as the potential miRNA targets of miRNA-205 [172]. The expression patterns of two target genes were negatively correlated with the miRNA-205 expression. Significant enrichments of CYR61 (p=0.050) and CTGF (p=0.007) mRNAs in HeLa cells with over-expression of miRNA-205 were observed. In addition, VEGF was indicated as a positive regulator of tumor growth that promoted tumor migration and invasion, and inhibits tumor apoptosis. Up-regulating of miRNA-205 by olmesartan could inhibit the VEGF-An expression, thus suppressed the tumor cell invasion [173].

MiRNA-346: The expression of miRNA-346 was significantly up-regulated in CC tissues and cell lines, as well as hTERT [174]. MiRNA-346 and -138 competitively bound to a same region in the 3'UTR of hTERT mRNA, the former promoted the expression and function of hTERT in CC cells to largely exert its cell growth-promotion effect. In addition, miRNA-346 was found to promote the migration and invasion of HeLa cells by directly increasing the
Regulation of miRNAs in radio-sensitivity and chemosensitivity in CC

Regulation of miRNAs in radio-sensitivity in CC: In general, surgery and radiotherapy remain the major treatment options for CC. As one of the most important treatments, the efficacy of radiotherapy was often limited by radio-resistance (inherent and acquired). It was reported that a considerable number of patients have been suffering from radiation insensitivity in clinical practice, and the 5-year survival rate was limited. Many patients have tumor recurrence because of radio-therapeutic resistance. However, the mechanism of radio-resistance was still unclear. Growing evidence suggested that many miRNAs were associated with radio-resistance, and radiation treatment of cancer cells would lead to the changes in expression of miRNAs, but the functions and potential molecular mechanism of these miRNAs in radio-resistance remain to be further studied (Table 4).

MiRNA-15a-3p: MiRNA-15a-3p was down-regulated in CC tissues and cell lines, and the expression of miRNA-15a-3p could be inversely correlated with pituitary tumor-transforming gene 1 (Pttg1) expression. Meanwhile, miRNA-15a-3p up-regulation was also significantly correlated with adverse clinicopathological characteristics, poor overall and progression-free survival, and poor prognosis. MiRNA-15a-3p inhibited Pttg1 expression in CC cells through directly binding and inhibition on 3'-UTR of Pttg1 mRNA [179]. Thus inhibited the CC cell invasiveness and metastasis. In addition, miRNA-15a-3p up-regulation was significantly correlated with PTEN down-regulation. Inhibition of miRNA-15a-3p repressed cell proliferation and growth by directly targeting PTEN [180]. Furthermore, down-regulation of miRNA-15a-3p expression arrested cell cycle in G1 phase, and suppressed cell proliferation and cell growth in CC cell lines.

MiRNA-501: MiRNA-501 was up-regulated in CC tissues. Over-expression was positively correlated with poor differentiation, tumor size, FIGO stage, and lymph node metastasis. In addition, miRNA-501 promoted cell proliferation, migration, and invasion, but suppressed the apoptosis of CC cells through down-regulating cyldinomatosis (CYLD) and activating NF-κB p65 [181]. Additionally, NF-κB p65, phosphorylated p65, and Bcl-2 expressions were all up-regulated significantly by miRNA-501, but Bax was down-regulated. These findings indicated that miRNA-501 suppressed CC cell apoptosis possibly via activation of NF-κB p65 and enhanced Bcl-2 mediated by inhibiting the expression of CYLD.

MiRNA-590-5p: MiRNA-590-5p was identified to be up-regulated in CC tissues and cell lines, and frequently down-regulated in these cancers. Moreover, miRNA-590-5p was down-regulated in CC tissues and cell lines, and frequently down-regulated in these cancers. The expression of miRNA-590-5p suppressed CC cell apoptosis significantly by miRNA-590-5p, but Bax was down-regulated. These findings indicated that miRNA-590-5p suppressed CC cell apoptosis possibly via activation of NF-κB p65 and enhanced Bcl-2 mediated by inhibiting the expression of CYLD.

MiRNA-361: Homo sapiens miRNA-361 stem-loop encodes two miRNAs, including miRNA-361-3p and -361-5p. Results demonstrated that preserved miRNA-361-3p expression was correlated with better primary therapy responses, lower ratio of lymphovascular invasion, recurrence, and death [176]. Thus, miRNA-361-3p may be a valuable prognostic biomarker for CC. Sclerostosis 1 (SOST), Metastasis-Associated protein 1 (MTA1), Transferrin Receptor protein (TFRC), and YAP1 were considered to be the potential genes, which were involved in modulating CC cell invasion, migration, and drug sensitivity. More studies are needed to verify the potential regulative effect of miRNA-361-3p on the expression of the genes above in the future. Furthermore, miRNA-361-5p was found to be up-regulated in CC cells and acted as an oncogene. MiRNA-361-5p was demonstrated to promote cell proliferation and invasion of CC cells, high expression of it is closely related to lymph node metastasis (p=0.021) and stromal invasion [177]. It was noteworthy that over-expression of miRNA-361-5p enabled the CC cells to obtain mesenchymal characteristics correlated with invasive and metastatic behavior in vitro and in vivo. In addition, there is a significant association between miRNA-361-5p and activated Wnt/β-catenin pathway in human CC cells, indicating that miRNA-361-5p promotes cell migration and invasion through the Wnt/β-catenin pathway.

MiRNA-378: MiRNA-378 expression level was significantly up-regulated in CC tissues. Re-expression of miRNA-378 dramatically promoted tumor migration, invasion, and metastasis in vitro. Autophagy-related protein 12 (ATG12), as a member of the ATG family correlated with autophagy, has been confirmed as a direct target of miRNA-378 and its expression could be down-regulated by miRNA-378 [178]. Over-expression of miRNA-378 decreased ATG12 expression in CC cells. Moreover, CCND1 and pRB were also down-regulated by miRNA-378, which controls the CC progression through regulating G1 phase and G1-S point of cell cycle, respectively.

MiRNA-494: MiRNA-494 was up-regulated in CC tissues and cell lines, and the expression of miRNA-494 was inversely correlated with pituitary tumor-transforming gene 1 (Pttg1) expression. Meanwhile, miRNA-494 up-regulation was also significantly correlated with adverse clinicopathological characteristics, poor overall and progression-free survival, and poor prognosis. MiRNA-494 inhibited Pttg1 expression in CC cells through directly binding and inhibition on 3'-UTR of Pttg1 mRNA [179]. Thus inhibited the CC cell invasiveness and metastasis. In addition, miRNA-494 up-regulation was significantly correlated with PTEN down-regulation. Inhibition of miRNA-494 repressed cell proliferation and growth by directly targeting PTEN [180]. Furthermore, down-regulation of miRNA-494 expression arrested cell cycle in G1 phase, and suppressed cell proliferation and cell growth in CC cell lines.

MiRNA-944: MiRNA-944 was confirmed up-regulated in CC tissues, and played an oncogenic role in CC cells through promoting cell proliferation, migration, and invasion, but had no effect on cell apoptosis. HECT domain ligase 2 (HECW2) and S100P binding protein (S100BP) were validated as the direct targets of miRNA-944 by binding to the 3'-UTR of both of them [185].
regulation of miRNA-18a inhibited the level of ataxia-telangiectasia mutated and attenuated DNA double-strand break repair after irradiation, which re-sensitized the CC cells to radiotherapy through inducing apoptosis by targeting the 3'-UTR of the Ataxia Telangiectasia-Mutated (ATM) gene [187], thus suppressed the expression of ATM. Meanwhile, miRNA-18a may be a novel biomarker for predicting the radio-sensitivity in CC treatment.

MiRNA-132: MiRNA-132 was down-regulated in CC tissues. Recent evidence indicated that radio-sensitivity may result from enhanced DNA repair; this is due to the radiotherapy inducing tumor cell death partly through damaging DNA. Additionally, over-expression of Bmi-1 has been thought as a marker of poor prognosis and tumor cell migration in CC, and contributes to radio-resistance in CC and other cancers. It was reported that miRNA-132 could sensitize CC cells to radiation through down-regulating Bmi-1 [188]. The results showed that miRNA-132 enhanced the radio-sensitivity of CC cells through inducing cell apoptosis and promoting proliferation.

MiRNA-136: As a down-regulated miRNA, miRNA-136 was reported to reduce radiation resistance of CC cells via its effect on apoptosis. It was found that miRNA-136 promoted apoptosis and radio-sensitivity in CC by targeting E2F1 through the NF-kB signaling pathway [35].

MiRNA-145: MiRNA-145 was down-regulated and promoted the radio-sensitivity of CC cell via silencing of OCT4, over-expression of miRNA-145 significantly reduced post-irradiation cell viability of CC cells and enhanced its post-irradiation apoptosis rate [189]. Moreover, it was proved that miRNA-145 targeted the DNA damage repair-related gene Helicase-like Transcription Factor (HLTF), which was involved in radio-resistance [87].

MiRNA-181a: MiRNA-181a was up-regulated in CC specimens and cell lines that were insensitive to radiotherapy, which was identified as a critical contributor to radio-resistance in CC. Recent study showed that miRNA-181a conferred radio-resistance through targeting the 3'-UTR of Protein Kinase C Delta (PRKCD) gene [190]. The effect of miRNA-181a on radio-resistance was mediated by its negative regulation of the expression of PRKCD via targeting the 3'-UTR of PRKCD gene.

MiRNA-218: MiRNA-218 was not only associated with tumor progression and poor prognosis of CC, but also played an important role in the radio-sensitivity of CC cells. Loss of miRNA-218 could be used to predict the radio-resistance of the primary CC cells (R2=0.652, p<0.001). Over-expression of miRNA-218 enhanced the radio-sensitivity in CC cells by promoting the radiation-induced apoptosis via up-regulating the expression of caspase-3 [191]. In addition, combination of miRNA-218 over-expression and radiation showed better effects on inhibiting the tumor growth in vivo. Both in vitro and in vivo, over-expression of miRNA-218 significantly promoted radiation related apoptosis, accompanied with the accumulation of both cleaved caspase-3 and cleaved PARP.

MiRNA-320: The expression of miRNA-320, located on chromosome 8q21.3, which was confirmed to be markedly down-regulated in radio-resistant CC cell line C33AR. Over-expression of miRNA-320 enhanced C33AR radio-sensitivity by targeting β-catenin through Wnt/β-catenin signaling pathway. The activation of the Wnt signaling pathway has been consider as a vital radio-protective mechanism in irradiated cancer cells. These finding proved that miRNA-320 may be a potential biomarker of radio-sensitivity in CC [192].

### Regulation of miRNAs in chemo-sensitivity in CC:
Chemosensitive drug resistance, as the main cause of treatment failure, remains a major problem in the treatment of CC for not only conventional chemo-therapeutic agents, but also the novel biological ones. Generally, CC chemo-therapeutic drug resistance mainly includes two categories: intrinsic and acquired resistance. The former refers to CC cells can be insensitive to drug before the treatment, but the latter refers to CC cells are initially sensitive and gradually acquire resistance during treatment [193]. Notably, acquired chemoresistance is one of the vital causal factors in cancer death. Although extensive literature has shown that aberrant miRNA expression is closely associated with chemo-resistance by targeting genes related to chemo-sensitivity or chemo-resistance the specific chemo-resistance-related miRNAs and their underlying molecular mechanisms are still largely unclear, which is shown in (Table 5).

**MiRNA-21:** As reported above, miRNA-21 plays an important role not only in cell proliferation, invasion, and apoptosis, but also in chemo-resistance of CC. Cancer susceptibility candidate 2 (CASC2), as a long non coding RNA, which was found to be down-expressed in the cisplatin-resistant CC tissues. It has recently been reported that there is a close interaction between long non coding RNA and miRNAs. Over-expression of CASC2 could sensitize cisplatin-resistant CC cells to cisplatin by direct suppressing miRNA-21, thus the interaction between CASC2 and miRNA-21 regulated the chemo-sensitivity to cisplatin based chemo-therapy through up-regulating PTEN expression [51]. Moreover, latest study indicated that the gene polymorphisms of rs1292037 (A>G) locus in miRNA-21 were associated with chemo-resistance to cisplatin plus paclitaxel [194].

**MiRNA-30a:** There was a significant down-regulation expression of miRNA-30a in CC cells after cisplatin treatment. The effect of miRNA-30a on enhancing HeLa cell chemo-sensitivity was believed not due to abnormal p53 functions in HeLa cells. The expression of miRNA-30a in various cancer cell lines was decreased after cisplatin or taxol treatment, but up-regulated expression of miRNA-30a inhibited

### Table 4: miRNAs involvement in cell radio-sensitivity and -resistance in CC and their target genes.

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Status</th>
<th>Target gene</th>
<th>Types of radiation sources</th>
<th>Effect</th>
<th>miRNA</th>
<th>Status</th>
<th>Target gene</th>
<th>Types of radiation sources</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>miRNA-15a-3p</td>
<td>Down</td>
<td>TDP52</td>
<td>X-ray</td>
<td>enhance radio-sensitivity [186]</td>
<td>miRNA-145</td>
<td>Down</td>
<td>HLTF/OCT4</td>
<td>Co-gamma ray</td>
<td>enhance radio-sensitivity [87, 189]</td>
</tr>
</tbody>
</table>

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beclin-1-dependent autophagy and increased the chemo-sensitivity of multiple cancer cells, including CC cells [195]. Notably, the chemotherapeutic treatment-induced autophagy markedly decreased the sensitivity of cancer cells to chemo-therapeutic agents.

MirRNA-125a: MirRNA-125a was one of most markedly down-regulated miRNAs in paclitaxel-resistant cells, which also possessed cisplatin resistance. It was proved that up-regulation of miRNA-125a sensitized paclitaxel-resistant cells to both paclitaxel and cisplatin in vitro. Therefore, there was a negative association between miRNA-125a expression and chemo-resistance. STAT3 was demonstrated as the target gene of miRNA-125a, which contributed to tumorigenesis and chemo-resistance by regulating apoptosis via promoting Bcl-2 and Bcl-xl expression [196]. The study confirmed that over-expression of miRNA-125a could promote cell apoptosis; suppress apoptosis-related proteins by directly binding to the 3'UTR of STAT3 and suppressing its expression. Additionally, CC patients with low miRNA-125a expression had shorter chemotherapy-induced progression-free survival and overall survival.

MirRNA-126: MirRNA-126 expression in CC tissues was significantly decreased compared with that in normal ones. It was reported that over-expression of C-FLIP like inhibitory protein (C-FLIP) was induced by the down-regulation of miRNA-126 in TNF-related apoptosis-inducing ligand (TRAIL)-resistant CC cells (HeLa-TR and SiHa-TR). Up-regulation of miRNA-126 enhanced the sensitivity of HeLa-TR and SiHa-TR cells to TRAIL by down-regulating the expression of C-FLIP. In addition, miRNA-126 increased the sensitivity of HeLa-TR and SiHa-TR cells to TNF-α and FasL [197]. The protein of C-FLIP was down-regulated by miRNA-126, which is the cellular antagonist to caspase-8. The cross-resistance to TNF-α and FasL could be decreased by treating with miRNA-126. Moreover, up-regulation of miRNA-126 suppressed CC cell proliferation, but increased the sensitivity to bleomycin by significantly reducing the IC50 of the agent [198]. These results indicated that miRNA-126 may be as a novel target for CC treatment.

Table 5: miRNAs involvement in cell chemo-sensitivity and -resistance in CC and their target genes.

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Target gene</th>
<th>Chemotherapeutic agents</th>
<th>Effect</th>
<th>miRNA</th>
<th>Target gene</th>
<th>Chemotherapeutic agents</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>miRNA-30a</td>
<td>Down</td>
<td>Beclin-1</td>
<td>Cisplatin</td>
<td>Enhance chemo-sensitivity [195]</td>
<td>miRNA-506</td>
<td>Down</td>
<td>Cisplatin/paclitaxel</td>
</tr>
<tr>
<td>miRNA-125a</td>
<td>Down</td>
<td>STAT3</td>
<td>Cisplatin/paclitaxel</td>
<td>Enhance chemo-sensitivity [196]</td>
<td>miRNA-664</td>
<td>Down</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>miRNA-126</td>
<td>Down</td>
<td>-</td>
<td>Bleomycin</td>
<td>Enhance chemo-sensitivity [198]</td>
<td>miRNA-1284</td>
<td>Down</td>
<td>HMGB1</td>
</tr>
<tr>
<td>miRNA-218</td>
<td>Down</td>
<td>Rictor</td>
<td>Cisplatin/carboplatin/rapamycin</td>
<td>Enhance chemo-sensitivity [202-204]</td>
<td>miRNA-210</td>
<td>Up</td>
<td>SMAD4</td>
</tr>
<tr>
<td>miRNA-224</td>
<td>Down</td>
<td>-</td>
<td>Paclitaxel</td>
<td>Enhance chemo-sensitivity [206]</td>
<td>miRNA-375</td>
<td>Up</td>
<td>E-cadherin</td>
</tr>
<tr>
<td>miRNA-49</td>
<td>Down</td>
<td>TKT</td>
<td>Cisplatin</td>
<td>Enhance chemo-resistance [209]</td>
<td>miRNA-629</td>
<td>Up</td>
<td>RSU1</td>
</tr>
</tbody>
</table>

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them significantly suppressed the level of c-Myc. Interestingly, it is believed that there is a balance between p53 and c-Myc in CC cells, the regulatory pathway between them is highly complex, which is not a simple linear pathway, but a sophisticated network.

MiRNA-181a: MiRNA-181a was significantly up-regulated in CC specimens that were resistant to chemo-therapeutic agents. It was found that miRNA-181a markedly suppressed the therapeutic response of CC cells to cisplatin through down-regulating the expression of PRKCD both in vitro and in vivo [200]. MiRNA-181a may enhance the chemo-resistance of CC cells by acting as an oncogene. Moreover, PRKCD activity was considered to be needed for apoptosis induced by DNA damaging drugs, including cisplatin, doxorubicin, cytosine arabinoside, and etoposide. Thus, the miRNA-181a-PRKCD interaction may be a biomarker for predicting chemosensitivity to chemo-therapy agents in CC patients.

MiRNA-210: MiRNA-210 was over-expressed in various cancers including CC, and played multiple roles in carcinogenesis. It was found that natural compound 1’ S-1’ - Acetoxychavicol Acetate (ACA) down-regulated the expression of miRNA-210 in CC cells. Suppression of miRNA-210 expression increased the sensitivity of CC cells to ACA through inhibiting cell proliferation and inducing apoptosis. SMAD4 was identified as a target of miRNA-210, the protein expression of it was down-regulated by miRNA-210 over-expression [201]. These studies indicate that combination of miRNAs and natural compounds may be novel strategies in the treatment of CC.

MiRNA-214: MiRNA-214 has been confirmed to be aberrantly expressed in human tumors and show various roles in cancer development. Previous studies have demonstrated that miRNA-214 is frequently down-regulated in CC tissues and inhibits cell proliferation, migration, and invasion. Apoptosis induced by miRNA-214 was associated with up-regulated expression of Bax, caspase-3, -8, and -9. The ectopic expression of miRNA-214 significantly decreased CC cell survival and promoted cells sensitivity to cisplatin through directly down-regulating the expression of Bcl212, but up-regulated the expressions of Bax, caspase-3, -8, and -9, which indicated that over-expression of miRNA-214 induced the apoptosis of CC cells through both extrinsic pathway and intrinsic pathway [113]. Additionally, Bcl212 was found to be up-regulated and promote cell survival and resistance to cisplatin in CC.

MiRNA-218: MiRNA-218 not only played an important role in tumor proliferation, metastasis, and radio-sensitivity, but also enhanced chemo-sensitivity of CC cells to cisplatin in vitro through its target, rapamycin insensitive companion of mTOR (Rictor), which was considered as cell apoptosis as a measure of chemo-sensitivity [202]. The underlying mechanism is blocking the AKT-mTOR signaling pathway. The expression of miRNA-218 was negatively associated with the mRNA level of Rictor in primary CC cells. Furthermore, it was found that low expression of miRNA-218 was correlated to resistance to carboplatin in primary CC cells. Tumors where miRNA-218 expression was restored were more sensitive to carboplatin than those with relatively down-regulated expression of miRNA-218. Additionally, over expression of miRNA-218 markedly decreased the level of Rictor and promoted the growth-inhibiting, cell cycle arrest, and apoptosis induced by rapamycin in vitro and in vivo [203,204], thus enhanced chemo-sensitivity of CC cells to rapamycin. These finding provided a strong arguments for the development of a novel therapy for CC based on miRNA-218, especially for patients with a down-expressed miRNA-218 level.

MiRNA-224: MiRNA-224 over-expression was correlated with aggressive progression and poor prognosis in CC [205]. MiRNA-224 was significantly down-expressed in CC cells treated by paclitaxel in a dose-dependent manner. Over-expression of miRNA-224 facilitated paclitaxel sensitivity against CC cells, the IC50 value was decreased in CC cells with up-regulation of miRNA-224 compared with miRNA-negative control (p<0.0001) [206]. These studies indicate that miRNA-224 may play a potential role in the development of drug resistance in CC and might act as a predictor for paclitaxel treatment or a therapeutic target in CC therapy.

MiRNA-375: MiRNA-375 showed consistent up-regulating expression levels across paclitaxel-treated CC cells and tissues. The association between miRNA-375 and cancer was believe to be a complex and cancer-specific relationship, the function of miRNA seems to be cancer specific and chemo-therapeutic agent specific. The expression of miRNA-375 was up-regulated by paclitaxel in a clear dose-dependent manner. Forced over-expression of miRNA-375 in CC cells reduced paclitaxel sensitivity in vitro and in vivo [207]. Emerging evidences indicated that miRNA and EMT play an important role in the chemo-resistance in cancer. Paclitaxel transiently up-regulated the expression of miRNA-375, inhibited cell proliferation, induced the transition from epithelial to mesenchymal phenotype, and consequently decreased paclitaxel sensitivity [208]. Forced over-expression of miRNA-375 inhibited the expression of E-cadherin by a directly targeting pathway, which resulted in paclitaxel resistance. These findings indicate that over-expression of miRNA-375 induced by paclitaxel facilitates EMT process through directly targeting E-cadherin, proliferation suppression, and consequently lead to chemo-resistance in CC cells. These findings suggest that a reversion of miRNA-375 or E-cadherin expression may be a novel therapeutic method for eliminating chemo-resistance in CC.

MiRNA-497: MiRNA-497 was significantly decreased in chemotherapy-resistant CC cells. Transketolase (TKT), as a direct target of miRNA-497, could be significantly down-regulated by treating with it. The miRNA-497/TKT axis was found to modulate the glutathione (GSH) and Reactive Oxygen Species (ROS) levels, which subsequently enhanced cisplatin chemo-resistance in CC. Mechanistically, cisplatin chemo-sensitivity induced by the miRNA-497/TKT axis was related to GSH depletion and ROS generation [209].

MiRNA-506: MiRNA-506 was down-regulated in CC cell lines. Up-regulation of miRNA-506 expression remarkably increased chemo-sensitivity of Caki and SiHa cells to both cisplatin and paclitaxel. [48].

MiRNA-629: MiRNA-629 is up-regulated in various cancers, including CC, and its expression was changed in ACA/cisplatin-treated CC cells [210]. Suppression of miRNA-629 expression enhanced the sensitivity of CC cells to ACA through inhibiting cell proliferation and promoting apoptosis via directly targeting ras suppressor protein 1 (RSU1). Over-expression of miRNA-629 down-regulated was the protein expression of RSU1 [211].

MiRNA-664: MiRNA-664 was down-regulated in both CC tissues and cell lines. Up-regulation of miRNA-664 expression significantly enhanced CC cells chemo-sensitivity to cisplatin [139]. The underlying mechanisms and target sites of miRNA-506 increasing chemo-sensitivity of CC cells to cisplatin remain to be investigated.

MiRNA-1284: MiRNA-1284 expression was down-regulated in CC tissues and cells. Up-regulation of miRNA-1284 not only inhibited
proliferation and invasion, but also promoted apoptosis of CC cells. Moreover, up-regulation of miRNA-1284 increased sensitivity of CC cells to cisplatin by down-regulating HMGB1 [212].

Conclusion

In summary, extensive literature suggest that miRNAs have played multiple roles in diagnose, treatment, radio-sensitivity, chemosensitivity, and chemo-resistance, mainly through their targeting of related genes and interactions with various signaling pathways. In the present comprehensive review, we collected 110 dysregulated miRNAs and 125 validated targets in CC through literature search. We analyzed miRNAs on the basis of expression status, functional classification, target gene, and molecule mechanisms. This review indicates that miRNAs affect various biological pathways in CC and can be developed for CC diagnosis, therapy, and prognosis. More studies need to be conducted to further explore therapeutically important miRNAs for CC treatment. Next generation sequencing technology will allow rapid development of miRNA in CC. More novel miRNAs will be identified and paint a more comprehensive picture of miRNA expression patterns in CC. Such a picture will improve our understanding on the molecular mechanisms underlying the phenotypes of CC. The next challenge is to identify the regulation relationships among miRNAs, target genes, and target proteins, and promote the wide application of miRNAs in the prevention, diagnosis, treatment, and prognosis of CC.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (31401483) and the Post-Doctoral Fund of Heilongjiang Province (LBH-Z14098). The authors also are thankful to the National Science Foundation of China (31401483) and the Post-Doctoral Fund of Heilongjiang Province (LBH-Z14098).

References


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