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Review

The roles and clinical significance of microRNAs in cervical cancer

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Summary. Cervical carcinogenesis induced by persistent human papillomavirus (HPV) infection represents a stepwise progression from precursors to invasive cervical cancer. Accumulated evidence has shown aberrant expression of microRNAs (miRNAs) in cervical cancer tissues and cells. Further studies reveal that miRNAs play key roles in the initiation and progression of cervical cancer, via specific signaling pathways, including E6-p53, E7-pRb, phosphoinositide-3 kinase (PI3K)-Akt, Notch, Wnt/β-catenin, and Hedgehog pathways. Some studies demonstrate that miRNAs might serve as biomarkers or therapeutic targets, presenting a potential prospect in clinical practice. All results provide new insights into the function of miRNAs and the pathogenesis of cervical cancer induced by viral oncoproteins. New approaches for miRNA-based prevention and management for cervical cancer will be developed in the future.

Key words: Cervical cancer, Human papillomavirus, MicroRNA, Signaling pathway

Introduction

Cervical cancer is one of the most common cancers and one of the major causes of cancer-related deaths in women worldwide. About 76% of all cases occur in developing countries where prevention and control of cervical cancer are still insufficient (Forouzanfar et al., 2011).

Human papillomavirus (HPV) infection is a necessary but not sufficient factor during the carcinogenesis of cervical cancer. Persistent high-risk HPV (HR-HPV) infection has been found to be consistently and strongly associated with high-grade cervical intraepithelial neoplasia (CIN), which is considered as an essential event for the progression to cervical cancer. HPV-16 and HPV-18 are the most frequent genotypes that are responsible for more than 70% of all cervical cancer cases. HR-HPV E6 and E7, the two early viral genes, have been shown to be vital pathogenic factors in HPV-associated cervical cancer (zur Hausen, 2002), and E6 and E7 oncoproteins functionally inactivate the tumor suppressor protein p53 and pRb and induce immortalization and malignant transforming of the squamous epithelial cells (Hawley-Nelson et al., 1989; Münger et al., 2002). In addition, the other involved cellular targets include telomerase and PDZ proteins for E6 and the Rb family proteins, along with p21 and p27 for E7 (Narisawa-Saito and Kiyono, 2007; Wise-Draper and Wells, 2008) E6-p53 and E7-pRb pathways are regarded as two classic pathways in the pathogenesis of HPV-related cervical cancer. However, explanations to some consequent events in HPV-infected cells and detailed mechanisms in the development and progression of cervical cancer are still unclear.

MicroRNAs (miRNAs, miRs) comprise an abundant class of endogenous, small non-coding RNAs that modulate gene expression post-translationally through binding to respective target mRNAs. It is demonstrated that miRNAs can both up- and down-regulate protein expressions. Bioinformatics studies have estimated that miRNAs may regulate 30% of all human genes and each miRNA can control hundreds of gene targets. Therefore,

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miRNAs form a complex network that tightly interacts with gene regulatory signaling pathways to perform basic biological processes such as cellular differentiation, proliferation and programmed death (Davalos and Esteller, 2010). Recent studies have also demonstrated that miRNAs participate in viral infection and cancer development, such as cervical cancer.

Aberrant expression and roles of miRNAs in cervical cancer

Genome-wide profiling of miRNA signatures indicates that aberrant miRNA expression is common in cancers. Some large-scale analyses of miRNA expression signatures were performed in cervical tissues or cell lines (Table 1). For example, Lui et al. (2007) found reduced expression of miR-143 and increased expression of miR-21 in cervical carcinoma cell lines compared to normal cervical samples. Lee et al. (2008) showed that miR-149 and miR-203 expressions were down-regulated while miR-9, miR-127, miR-199s, and miR-214 expressions were up-regulated in cervical cancer tissues compared to normal cervix controls. Wang et al. (2008) found decreased expressions of miR-23b, miR-34a, miR-101, miR-143, miR-145, miR-218, and miR-424 and increased expressions of miR-15a, miR146a, and miR-223 in cervical cancer tissues compared with normal cervical samples. In addition, our previous miRNA signature study demonstrated altered expressions of 31 miRNAs, including down-regulated miR-218, miR-424 miR-375, and miR-100, and up-regulated miR-15b and miR-93 (Li et al., 2011b). All global miRNA analyses indicate different miRNAs expression profiling. The involved reasons may be

Table 1. Aberrantly expressed miRNAs in tissues of cervical cancer and precursors.

Authors and years	Down-regulated miRNAs	Up-regulated miRNAs	Potential use
Lui et al., 2007	let-7a-c, miR-23b, miR-143, miR-196b	miR-21	Diagnosis
Martinez et al., 2008	miR-126, miR-143, miR145, miR-195, miR-218, miR-368, miR-497	miR-182, miR-183, miR210	Diagnosis
Wang et al., 2008	miR-23b, miR-34a, miR-101, miR-143, miR145, miR-218, miR-424	miR-15a, miR146a, miR-223	Diagnosis
Lee et al., 2008	miR-149, miR203	miR9, miR127, miR-199b,miR-199s, miR-214	Diagnosis
Li et al., 2010	miR-34a,		Diagnosis
Hu et al 2010	miR-200a	miR-9	Poor prognosis
Deftereos et al., 2011		miR-21	Diagnosis
Li et al., 2011a	miR-100		Diagnosis
Li et al., 2011b	Let-7b, miR-10b, miR-29a miR-99a, miR-125b, miR-126, miR-218, miR-375, miR-424	miR-15b, miR-16, miR-17, miR-20a, miR-20b, miR-93, miR-106a, miR-155, miR-224	Diagnosis
Wang et al., 2011a	miR-375		Diagnosis, poor prognosis
Tian et al, 2011	miR-372		Diagnosis
Ma et al., 2012	miR-143, miR-145, miR-203, miR-424, miR-572	miR-20a, miR-20b, miR-21, miR-141, miR-200a, miR-224, miR-15a, miR-146a, miR-155	Diagnosis
Li et al., 2012	miR-218		Chemoresistance
Cheung et al., 2012	miR-203	miR-518a, miR-34b, miR-34c, miR-20b, miR-338, miR-9, miR-512-5p,	Diagnosis
Shi et al., 2012	miR-145		Chemoresistance
Liu et al., 2012		miR-15b,miR-16	Chemoresistance
Luo et al., 2013	miR-497		Diagnosis
Shen et al., 2013a		miR-224	Poor prognosis
Shen et al., 2013b		miR-375	Chemoresistance
Wang et al., 2013b		miR93, miR200a	Poor prognosis
Zhao et al., 2013a,b	miR-203	miR-20a	Poor prognosis
Xu et al., 2013	miR-424		Diagnosis, poor prognosis
Wang et al., 2013a		miR-214	Chemoresistance
Chen, et al., 2013		miR-1246, miR-2392, miR-3147, miR-3162-5p and miR-4484	Poor prognosis
Chen et al., 2014a	miR-143		Poor prognosis
Chen et al., 2014b		miR-181a	Chemoresistance
Wang et al., 2014a		miR-25, miR-92a, miR-378	Diagnosis
Liang, et al., 2014		miR-125	Poor prognosis
Yang, et al., 2014	miR-126		Poor prognosis
Wang et al., 2014b			
Zheng et al., 2015		miR-31	Poor prognosis
*Tian et al., 2014	miR-375, miR-424, miR-218		Screening
Gocze et al., 2015	miR-34a	miR-27a	Diagnosis
Zhou et al., 2015	miR-92a		Diagnosis
Wang et al., 2015; Ye et al., 2015	miR-145		Poor prognosis

*, miRNAs detected in cervical exfoliated cells.

complicated, including the heterogeneity of specimens, such as cells or tissues, cervical low or high grade lesions, and geography areas or human races (Li et al., 2014), and the difference of specimen collection, preservation, and detection methods (How et al., 2015). Therefore, gene function studies are necessary to identify miRNA roles in cervical cancer pathogenesis.

Accumulated evidence has shown that aberrantly expressed miRNAs act as tumor suppressive or oncogenic miRNAs in cervical cancer pathogenesis or progression. For example, miR-424 presents potential tumor–suppressive characteristics by targeting CHK1 (Xu et al., 2013) which is a key factor for cellular response to DNA damage, governing G1/S, S and G2/M phase checkpoints (Bartek and Lukas, 2003), and participating in the progression of cervical cancer. The ectopic expression of miR-424 in human cervical cancer cell lines remarkably inhibits cell growth, enhances apoptosis, blocks G1/S transition, and suppresses cell migration and invasion (Xu et al., 2013). By contrast, miR-21 is overexpressed in cervical cancer and possibly promotes the malignant transformation of the cells by directly targeting CCL20 (Yao and Lin, 2012). miR-92a is significantly upregulated in cervical cancer tissues and cell lines, and promotes proliferation and invasion of cervical cancer cells by inhibiting FBXW7 expression (Zhou et al., 2015). Frequently observed dysregulated miRNA expression facilitates the investigation into the involved mechanisms.

miRNA-associated signaling pathways in cervical cancer cells

Based on the information on aberrantly expressed miRNAs in cervical cancer, various associated mechanisms are beginning to be understood. Recent studies demonstrated that possible signaling pathways involved in the expression and mechanisms of action of miRNAs include E6-p53, E7-pRb, phosphoinositide-3 kinase (PI3K)-Akt, Wnt/β-catenin, Notch, and Hedgehog pathways.

The E6-p53 pathway is one of the essential pathways in HPV oncoprotein-induced carcinogenesis of cervical cancer. p53 in cervical cancer is frequently wild type and can be degraded by E6 of high-risk types, inducing replication stress and thereby DNA damage. Accumulation of DNA damage and loss of DNA repair capability result in chromosome instability, which may contribute to the successful integration of viral DNA to host DNA. The miR-34 family is characterized as a p53 target gene (He et al., 2007) and plays key roles in several types of cancers. Subsequent studies show that knockdown of viral E6 expression in HPV16(+) or HPV18(+) cervical cancer cell lines by siRNAs leads to increased expression of p53 and miR-34a (Wang et al., 2009), and that ectopic miR-34 expression targets p18Ink4c (Wang et al., 2011b), suggesting that HR-HPV infection down-regulates miR-34a expression through viral E6 protein and degradation of p53 trans-activator. The inhibition of miR-34a expression induced by HR-HPV E6 in the p53-dependent pathway is probably an early-onset event in the development of cervical cancer, since the expression of pri-miR-34a is reduced both in cervical cancer tissues and precancerous lesions, even before morphologic changes (Li et al., 2010). In addition, miR-23b is found to be down-regulated by HPV 16 E6 through p53 mediation and consequently increases the expression of urokinase-type plasminogen activator (uPA) (Au Yeung et al., 2011), and miR-23b/uPA is confirmed to be involved in HPV-16 E6-associated cervical cancer development. miR-203 plays a role in epithelial cell biology by regulating p53 levels. HPV16 E6 affects miR-203 expression and reduces DNA damage dependent on p53 during proliferation and differentiation of human foreskin keratinocytes (McKenna et al., 2010). Overexpression of HPV16 E6 induced by cortisol effectively suppresses p53-dependent miR-145 up-regulation and cellular apoptosis (Shi et al., 2012). Although miR-34a, miR-23b, miR-203, and miR-145 are all regulated by E6 and dependent on p53, miR-218 is down-regulated by HPV16 E6 via targeting LAMB3, but not dependent on p53 (Martinez et al., 2008; Yamamoto et al., 2013). E6-induced cellular miRNA expression abnormality can be considered as the reforming of the microenviroment in host cells to benefit the survival of virus. However, some cellular miRNAs may try to eliminate or inhibit HPV infection and maintain a balance to benefit cell survival. Only two cellular miRNAs that target viral oncogenes have been found up to now. miR-375 directly binds to viral transcripts and reduces the expression of E6, leading to the elevation of p53 expression (Jung et al., 2014). miR-375 is the first discovered miRNA that directly targets and regulates viral oncogenic early protein. In HPV18-positive cervical cancer Hela cells, miR-129-5p regulates E6 expression by targeting 14-3-3zeta and SP1 genes (Zhang et al., 2013). The interaction between cellular miRNAs and HPV oncoproteins is important and complicated. Uncovering the relationship between HPV and miRNA can deepen understanding about the carcinogenesis of cervical cancer and provide new insights into the mechanisms by which HPV induces cervical cancer development at miRNA level.

E7-pRb is another essential pathway in HPV-induced cervical cancer. E7-mediated abrogation of pRb function maintains cell cycle activity, which is necessary for replication of productive virus in differentiated epithelial cells (Thomas et al., 1999) and indispensible for maintaining viral genome as episomes in undifferentiated cells (Longworth and Laimins, 2004). The E7-pRb pathway possesses the ability to regulate a subset of cellular miRNAs. It is shown that miR-203 is down-regulated by the expression of E7 (Melar-New and Laimins, 2010). E7 regulates the activation of mitogen-activated protein kinase and protein kinase C pathway and consequently influences miR-203 expression, which maintains cell cycle progression during cell proliferation by targeting ΔNp63 (Melar-New and Laimins, 2010). E7

also regulates the trans-activation of c-Myb and c-Myc and influences the expression of DLEU2, leading to alterative expression of miR-15/16 cluster. The expression of miR-15b (Zheng and Wang, 2011) is shown to be highly correlated with five selected E2F-induced genes (CCNA2, CCNB1, CCNB2, MSH6 and MCM7). Knockdown of HPV16 E7 results in decreased levels of miR-15b in CaSki cells (Myklebust et al., 2011). Expression of both miR-24 and miR-205 is impacted by E6 and/or E7 expression, which is possibly one of the mechanisms by which HPV oncoproteins disrupt the balance between proliferation and differentiation in keratinocytes (McKenna et al., 2014). Additionally, miR-205 expression is dependent on pRb expression induced by E7 activation. Similar to in the E6-p53 pathway, cellular miRNAs can also influence the expression of E7 protein. miR-375 (Jung et al., 2014) and miR-129-5p (Zhang et al., 2013) are the only two discovered miRNAs that are capable of inhibiting the expression of E7 oncoprotein, resulting in up-regulation of pRb. However, more studies are necessary to discover the relation between miRNAs and HPV.

PI3K signaling pathway, as a major pathway involved in cell growth and proliferation, plays an important role in the regulation of diverse cellular processes. It is revealed that miRNAs act as Akt activators or Akt effectors in this pathway. Tumor suppressor phosphatase and tensin homologue (PTEN) can block the formation of phosphatidylinositol-(3,4,5)-trisphosphate from phosphatidylinositol-4,5-bisphosphate and acts as a notable negative regulator of Akt that controls Akt activity. PTEN activity is frequently lost in many types of cancers, leading to increased cell survival and cell cycle progression. In addition, forkhead box, class O (FoxO) family, mouse double minute 2 homolog, p53, and mammalian target of rapamycin have been identified as Akt effectors. However, all these molecules in the pathway are shown to be the targets of miRNAs. For instance, miR-92 up-regulated by HPV16 E6 is able to affect PTEN protein expression (Yu et al., 2013). Furthermore, miR-125b directly targets phosphoinositide 3-kinase catalytic subunit delta, inhibits tumor growth and promotes the apoptosis of cervical cancer cells (Cui et al., 2012). miR-302-367 cluster directly down-regulates both cyclin D1 and AKT1, and indirectly up-regulates p27(Kip1) and p21(Cip1), leading to the suppression of proliferation (Cai et al., 2013). miR-133b targets MST2, CDC42 and RHOA, which subsequently result in the activation of AKT1 and ERK signaling pathways (Qin et al., 2012). Overexpression of miR-218 reduces cell proliferation, induces apoptosis through targeting AKT-mammalian target of rapamycin signaling pathway, and enhances chemo-sensitivity to cisplatin *in vitro* (Li et al., 2012). In addition, FOXO1 and p27(Kip1), two key effectors of PI3K/Akt signaling, are shown to be direct targets of miR-196a in promoting cervical cancer cell proliferation (Hou et al., 2014). Considering a key role of PI3K pathway in cell growth and proliferation, miRNAs involved in this pathway may become candidates as targets in cervical cancer therapy.

Previous reports have demonstrated that aberrant activation of the Wnt signaling pathway is involved in various human cancers, such as colorectal, gastric, melanoma, and cervical cancers. The activation of the canonical Wnt pathway has been regarded as a second hit, following viral oncoprotein primary attack, in the process of malignant transformation of immortal cells and HPV-related carcinogenesis (Uren et al., 2005). E6/E7 proteins suppress β-catenin ubiquitin degradation complex, resulting in β-catenin activation in virus-driven cervical carcinogenesis (Bonilla-Delgado et al., 2012). β-catenin is the key molecule in the Wnt pathway, and accumulated evidence has shown that β-catenin expression is partly regulated by specific miRNAs. For example, the expression of miR-200a, an epithelial-mesenchymal transition-associated tumor suppressor, is changed in cervical cancer tissues after altering the expression of Wnt/β-catenin signaling pathway members. miR-200a directly targets CTNNB1 (a gene that encodes β-catenin) and suppresses the activity of the Wnt/β-catenin signaling pathway (Su et al., 2012). miR-135a/seven in absentia homolog 1 (SIAH1)/β-catenin signaling is another regulatory mechanism in the transformation and progression of cervical carcinoma (Leung et al., 2014). miR-135a is found to be overexpressed in malignant cervical carcinoma tissues compared to precancerous lesions. Furthermore, miR-135a expression is negatively correlated with SIAH1 and β-catenin expression in the biopsied precancerous and cancerous lesions. Forced ectopic expression of miR-135a induces growth, proliferation, and invasion of NC104-E6/E7 (an HPV-16 E6/E7-immortalized cervical epithelial cell line) and Hela cells by directly targeting SIAH1, leading to β-catenin signaling activation (Leung et al., 2014). Therefore, miR-200a and miR-135 may be new candidate tumor suppressors that regulate the activity of the Wnt/β-catenin signaling pathway.

The Notch pathway is a highly conserved pathway that is identified as a double sword in the pathogenesis and progression of cervical cancer (Koch and Radtke, 2007). It has been revealed that Notch or Notch ligands are overexpressed in the early stage of cervical cancer tissues and exert tumor suppressive effects in HPV-positive cervical cancer (Wang et al., 2007). On the other hand, increased Notch expression promotes transformation and correlates with progression to cervical cancer (Veeraraghavalu et al., 2004). Notch-1 expression and activity are up-regulated by E6 and E7, and accelerate cell growth in cervical cancer (Weijzen et al., 2003; Veeraraghavalu et al., 2005). However, knowledge of miRNAs involved in Notch pathway in cervical cancer is still limited. miR-34a is the only known miRNA that targets Notch1 in cervical cancer (Pang et al., 2010), resulting in an activity change of downstream molecule Hes-1 in Notch signaling.

The Hedgehog pathway (Hh pathway) is a well-known developmental signaling pathway that controls

cell proliferation and differentiation during embryonic development, but is largely suppressed in adults. Aberrant activation of the Hh pathway is related to several human cancers. In cervical cancer and precursor lesions, the expression of all Hh-signaling molecules is greatly enhanced (Xuan et al., 2006). Although Hh signaling is not regulated directly by HPV early oncogenic proteins, Hh-activating mutations have been selected in HPV immortalized cells (Samarzija and Beard, 2012). A recent study shows that miR-506 is down-regulated in cervical cancer tissues and negatively regulates cervical cancer cell growth by targeting Gli3 gene (Wen et al., 2014), a key effecter of the Hedgehog pathway in organ development and cancer progression. It is believed that there must be more unknown miRNAs involved in Hedgehog pathway during cervical cancer pathogenesis and development.

The clinical significance of aberrant miRNA expression in cervical cancer and precursors

Based on the aberrant expression profiles of miRNAs in cervical cancer and precursors and the roles of miRNAs in the development and progression of cervical cancer, various studies are focused on the clinical significance of aberrant miRNA expression and the potential value of miRNA detection in screening, assistant diagnosis, and even therapy for cervical cancer (Table 1).

miRNAs could be ideal biomarkers of cancers due to their specific features, such as small and simple structures, stability, and easy detection. In a recent study, the expression of 202 miRNAs in micro-dissected high grade CIN (CIN2/3) and normal cervical epithelium were detected, including 12 highly differentially expressed miRNAs such as miR-518a, miR-34b, miR-34c, miR-20b, miR-338, miR-9, miR-512-5p, miR-424, miR-345, miR-10a, miR-193b, and miR-203, suggesting that the detection of these miRNAs could distinguish high-grade CIN or cervical squamous cell carcinoma from normal cervical epithelium (Cheung et al., 2012). Being consistent with miR-34a action as an early event in the development of cervical cancer, miR-34a is probably a valuable biomarker for predicting HPV infection outcome and distinguishing high-grade CIN from low-grade CIN. Li et al. reported that miR-34a is down-regulated in CIN-2-3 compared with CIN1 or normal cervical epithelial tissues (Li et al., 2010). miR-125b is probably another miRNA participating in the initial phase of cervical carcinogenesis, including inflammation and immune response against HPV infection (Wang et al., 2008). Evaluation of miR-125b expression in pathologically pre-neoplastic lesions could be helpful to identify HR-HPV persistent infection and cervical lesions progression. Aberrant miRNA expression in high-grade CIN suggests that miRNA may be utilized for cervical cancer screening. In view of higher sensitivity and negative predictive value, HPV testing has been recommended as a primary assay in cervical cancer screening. However, due to its lower specificity and positive predictive value, triage is necessary for HPV-positive women, and cytology is a preferred option. Recently, detection of miRNA expression in cervical exfoliated cells showed that compared with cytology triage, detection of the expression of single miR-424 or miR-375 or combined multiple-marker panels had higher sensitivity and negative predictive value, as well as comparable specificity and positive predictive value, for high-grade CIN identification in 1021 HPV-positive women from a clinic-based population, suggesting that miRNA detection may provide a new triage option for HPV-positive women (Tian et al., 2014).

As oncogenes or tumor suppressors, miRNAs not only participate in the initiation, but also encompass the progression in cervical cancer, suggesting that miRNAs may serve as predictors for evaluating cervical cancer prognosis. Lee et al. (2008) reported that increased miR-127 expression was significantly associated with lymph node metastasis in 31 patients with early-stage invasive squamous cell carcinomas. Hu et al. (2010) found that miR-200a and miR-9 regulated the metastatic potential and process of cancer cells, and miR-9 was involved in metabolic processes and maintains a high metabolic rate of tumor cells. Previous studies also showed that lower expression levels of miR-375 (Wang et al., 2011a), miR-100 (Li et al., 2011a), miR-424 (Xu et al., 2013), miR-497 (Luo et al., 2013) and miR-494 (Chen et al., 2015) were correlated with the progression of cervical cancer. Down-regulated miR-126 (Yang et al., 2014) and miR-145(Wang et al., 2015) were independently associated with the overall survival and could serve as independent poor prognostic factors for cervical cancer patients. In addition to tumor suppressive miRNAs, some oncogenic miRNAs, such as miR-224 (Shen et al., 2013a), miR-31 (Wang et al., 2014b), miR-20a (Zhao et al., 2013a,b), and miR-130a (He et al., 2014), were also found to present clinical significance in cervical cancer. Elevated expression of these miRNAs is correlated with poorer prognosis of cervical cancer patients. For instance, miR-224 up-regulation is associated with aggressive progression of cervical cancer and patients with higher miR-224 expression tend to have shorter overall survival (Shen et al., 2013a). In addition, higher expression of miR-130a is significantly associated with shorter disease-free survival (He et al., 2014). miR-31 overexpression is found to be significantly correlated with poorer prognostic factors, including higher International Federation of Gynecology and Obstetrics stage, node metastasis, vascular involvement and deep stromal invasion, and miR-31 is considered as an independent prognostic factor for cervical cancer (Wang et al., 2014b). Some recent reports also showed that the circulating level of miR-20a (Zhao et al., 2013a), miR-1246, miR-2392, miR-3147, miR-3162-5p and miR-4484 might be predictors for evaluating lymph node status in cervical cancer (Chen et al., 2013). miRNA detection may provide a new approach to guide the

treatment decision for cervical cancer patients.

As regulators of gene expression, miRNAs may be linked to chemo-resistance. Phuah et al. (2013) reported that aberrant expression of miRNAs (miR-138, miR-210, and miR-744) alters the sensitivity of cervical cancer cells to cisplatin. Paclitaxel is found to up-regulate miR-375 expression in cervical cancer cells in a dose-dependent manner *in vitro*, and the overexpression of miR-375 enhances resistance to paclitaxel both *in vitro* and *in vivo* by targeting cadherin 1 (Shen et al., 2013b). miR-181 is another miRNA that is related with drug resistance of cervical cancer. Overexpression of miR-181a enhances chemo-resistance to cisplatin by targeting protein kinase C delta (Chen et al., 2014b). In contrast to tumor suppressive miRNAs, oncogenic miRNA overexpression promotes drug sensitivity. For example, elevated expression of miR-145 (Shi et al., 2012), miR-155 (Lei et al., 2012), miR-214 (Wang et al., 2013a), miR-218 (Li et al., 2012), miR-15b and miR-16 (Liu et al., 2012) increase the sensitivity of cervical cancer cells to chemotherapy. Forced ectopic expression of miR-145 enhances mitomycin sensitivity and reverses glucocorticoid-induced chemo-resistance through influencing the mitomycin-induced apoptosis pathway. In addition, miR-155 suppresses epithelial-mesenchymal transition induced by EGF and increases chemo-sensitivity to cisplatin in Caski cells (Lei et al., 2012). Altered miRNA expression in drug resistance suggests that miRNAs might serve as potential therapeutic targets in cervical cancer.

Conclusions and future perspectives

Persistent HR-HPV infection is necessary, but not sufficient, in the initiation and progression of cervical cancer. Accumulated evidence has shown aberrant expression and role of miRNAs via specific signaling pathways in cervical cancer development. Some studies demonstrate that miRNAs might serve as biomarkers or therapeutic targets, presenting a potential prospect in clinical practice. However, further investigations are still needed. There is still no detailed map of interactions between viral oncoproteins and cellular signaling pathways. The application of miRNAs that play key roles in cervical cancer initiation or progression should be verified by various clinical trials. Nevertheless, the perspective is promising and a new approach of miRNA-based prevention and management for cervical cancer may be realized in the future.

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