Malaysian Journal of Medicine and Health Sciences (eISSN 2636-9346)

REVIEW ARTICLE

MicroRNAs in HPV-induced Cervical Cancer Carcinogenesis and Potential Biomarkers

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ABSTRACT

The prevalence of cervical cancer largely due to long-term high-risk human papillomavirus (HPV) infection continues to be a major global health concern. Despite the existence of effective preventive interventions such as HPV vaccination and cervical screening programs, the progression of HPV-induced cervical lesions to invasive cancer remains a significant concern. Over the past 10 years, microRNAs (miRNAs) have become one of the most important gene expression regulators, controlling a wide range of biological processes, including carcinogenesis. Understanding the complex regulatory network including miRNAs and their target genes can provide important insights into the molecular mechanisms driving cervical carcinogenesis. Using miRNAs' diagnostic, prognostic, and therapeutic potential may pave the way for personalized approaches to the treatment of HPV-induced cervical cancer, thereby improving patient outcomes. The objective of this review is to provide a comprehensive analysis of the critical role miRNAs play in the induction and progression of HPV-induced cervical cancer. An electronic search was performed through PubMed, Scopus and Science Direct with the following MeSH (Medical Subject Heading) term: human papillomavirus, cervical cancer and microRNAs. From the search, only studies with HPV-induced cervical cancer with miRNA dysregulation which involve in regulation of cervical cancer development and progression were included.
Malaysian Journal of Medicine and Health Sciences (2025) 21(1): 346-356. doi:10.47836/mjmhs.21.1.40

Keywords: Cervical cancer, MicroRNAs, MicroRNAs dysregulation, Human papillomavirus, Biomarkers

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INTRODUCTION

Cervical cancer is a significant public health issue, especially in less developed and undeveloped nations. It is the fourth most common cancer among women and is a main cause of cancer-related deaths globally [1]. Several studies indicate that cervical cancer remains a significant source of morbidity and mortality due to metastasis and recurrence, leading to ongoing concerns regarding poor prognosis. Histologically, cervical cancer can be either squamous cell carcinoma which represent around 80% of total cases or adenocarcinoma which account for about 20% [2,3]. The presence of human papillomavirus (HPV) infection is a significant risk factor for the development of cervical cancer. Even though, cervical cancer is not mainly triggered by HPV infection, most cases result from prolonged and persistent HPV infection. The manifestation of cervical cancer may occur 20 years or more after acquiring HPV. The diagnosis of cervical cancer typically involves a combination of screening, clinical evaluation, and confirmatory tests. Cervical cancer screening like Pap smear and HPV testing has made tremendous progress in lowering the incidence and mortality rates of the disease. However, these methods have several limitations related to sensitivity and specificity. Studies have found that the sensitivity of a Pap smear for detecting high-grade cervical lesions was about only 53% with 95% specificity. However, false positives can occur, leading to unnecessary follow-up tests and procedures. HPV test have higher sensitivity compared to Pap smear, however its has lower specificity (85%-90%) compared to the Pap smear [4]. This lower specificity can lead to more false-positive results. This can result in overdiagnosis and overtreatment, subjecting people to unnecessary medical procedures and costs. Discovery of potential biomarkers that are expressed in early stage and along the carcinogenesis pathway would be highly relevant for the development of more effective diagnostics cervical cancer.

HPV is a circular double-stranded DNA virus that is around 8 kilobases in size. The genome is composed of three functional regions of an upstream regulatory region (URR), early region (E) and late region (L). These regions make up the genome's three primary regions. The URR encompasses sequences that regulate the processes of transcription and replication of the virus. The early region comprises open reading frames (ORFs) encoding three regulatory proteins (E1, E2, and E4) and three oncoproteins (E5, E6, and E7) that play a role in both replication and cell transformation. The late region encodes for the L1 and L2 capsid proteins, which form the structure of the virion [5,6]. Until now there are over 200 different types of HPV, and 40 of them can infect and transform the cervical epithelium [7]. It can be classified as high risk or low risk based on its oncogenic potential.

Most HPV infections are transient and resolve within a period of 12-24 months. Persistent infection with oncogenic types of HPV is the main risk factor for the development of cervical dysplasia, which is also referred to as cervical intraepithelial neoplasia (CIN) at various stages (CIN1/CIN2/CIN3). CIN is a pathological disorder characterized by the presence of abnormal cells in the cervix, which can progress to cervical cancer. It is classified as a pre-cancerous state. Some cases of CIN might proceed to invasive cervical cancer if not treated. The process could take years or perhaps decades. CIN1 is a morphologic indication of HPV infection, and approximately 70-80% of CIN1 spontaneously regresses or becomes undetectable without treatment [8]. CIN2 is linked to a lower likelihood of getting cancer, whereas CIN3 is a pre-cancerous state that is more prone to recurrence[4]. Approximately 30% of CIN3 cases progress to invasion over a 30-year timeframe [8]. Infection with high-risk HPV (HR-HPV) is a prerequisite, but not the only factor, for the development of cervical cancer. HR-HPV DNA is detected in 99.7% of all cases and in a significant proportion of cases with high-grade neoplasia [9].

The carcinogenesis of cervical cancer is a multistep process of uncontrolled cellular division that includes the incorporation of the HPV gene as well as other cellular alterations and epigenetic factors. The carcinogenesis mechanism is only partially known. The overexpression of viral E6 and E7 proteins disrupts the cell cycle regulatory pathways, effectively inhibiting the products of the RB and TP53 immunosuppressant genes [10]. These pathways are necessary for development of pre-neoplastic intraepithelial state and progression to invasive cancer happens due to the accumulation of genetic abnormalities. The entire process is complex, encompassing a variety of genetic and epigenetic modifications. Recently, there has been a focus attention in the involvement of miRNA in carcinogenesis.

MiRNAs are small non-coding RNAs that typically consist of 18 to 22 nucleotides. They have been shown to influence gene expression by either cleaving mRNA or inhibiting its function [10,11]. In malignancies, miRNA's expression may be up- or down-regulated. Cervical cancer has been associated with altered miRNA expression due to both genetic abnormalities such as deletion, amplification, and point mutation, as well as epigenetic alterations such histone modifications and aberrations in DNA methylation. The role of the specific miRNAs and the mechanism by which they are deregulated is still largely unknown. Hence, there is significant interest in finding novel biomarkers for HPV-associated cervical cancer that have strong diagnostic and prognostic potential for early detection of cervical cancer. This review aims to provide a summary of the published literature on miRNAs and their involvement in the progression of cervical cancer.

HPV induced carcinogenesis

HPV induces carcinogenesis primarily through the actions of its oncogenes E6 and E7 as demonstrated in Fig.1. These two viral genes play a critical role in the transformation of normal cells into cancerous ones by disrupting key regulatory pathways involved in cell growth and apoptosis. In cervical cancer, the integration of HPV DNA into the host genome often disrupts the viral E2 gene, which normally regulates E6 and E7 expression. The loss of E2 function leads to the overexpression of E6 and E7, further driving the carcinogenic process.

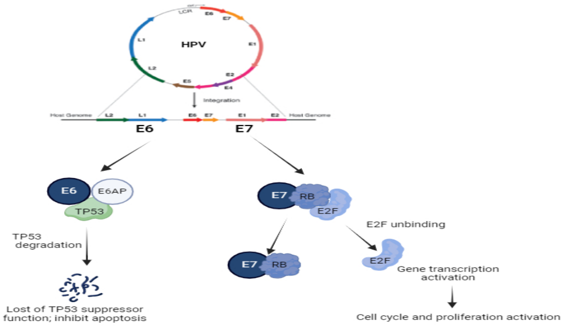

Fig. 1: HPV induced carcinogenesis by HPV oncogenes E6 and E7 inhibit tumour suppressor gene TP53 and RB. The E6 inhibits the tumor suppressor gene by binding to TP53, preventing cell apoptosis. Meanwhile, the E7 binds to the RB protein, causing the release of the E2F transcription factor, which subsequently activates the cell cycle and promotes cell proliferation.

The E6 protein binds to the p53 tumor suppressor protein, a crucial regulator of the cell cycle and apoptosis. Under normal circumstances, p53 responds to DNA damage by either halting the cell cycle to allow for DNA repair or inducing apoptosis if the damage is irreparable. When E6 binds to E6AP (E6-associated binding protein), a ubiquitin ligase causes a structural change in E6, enabling it to bind to TP53. This results in the development of a trimeric complex consisting of E6/E6AP/TP53 and promotes the ubiquitination and subsequent degradation of p53 [11]. This degradation prevents p53 from performing its protective functions, leading to unchecked cell division and the potential accumulation of further genetic mutations. In addition, E6 can augment the degradation of PDZ proteins, leading to changes in cell apoptosis, modulation of cell cycle checkpoints, activation of telomerase, and cell proliferation [12–14]. E6 also targets hDLG and hScrib, which have a role in cell transformation and progression of cancer caused by HPV [15].

While E7 is known to be associated with cellular tumour suppressor retinoblastoma protein (pRb). The E7 protein targets the pRb, another key regulator of the cell cycle. pRb normally binds to the transcription factor E2F, preventing it from activating genes required for the transition from the G1 to the S phase of the cell cycle. When E7 binds to pRb, it disrupts this interaction, leading to the release of E2F. E2F can then activate genes that drive the cell cycle forward, promoting uncontrolled cell proliferation [9, 16].

The association of the E6 and E7 oncogenes with microRNAs (miRNAs) is a significant aspect of HPV-induced carcinogenesis. HPV oncoproteins, particularly E6 and E7, can modulate the expression of various miRNAs, thereby influencing the cellular environment to favor malignant transformation.

miRNA biogenesis

miRNAs, which are single-stranded RNAs, belong to a group of non-coding RNAs that participate in post-transcriptional gene silencing by degrading mRNA or inhibiting translation [17,18]. miRNAs are synthesized in the nucleus following transcription by the RNA polymerase II enzyme [10,19]. Most miRNA genes are found in noncoding intergenic areas, although they can also be found in exonic or intronic regions in both the sense and antisense orientations. Additionally, miRNAs can be independently transcribed by their own promoter [20]. MiRNAs are categorized into families according to their sequence similarity and function. They can be present in the genome either as individual units or as clusters[18]. It is thought that single miRNA has a potential to negatively regulate hundreds of thousands of target genes. The synthesis of miRNA can be categorized into two main pathways: a canonical pathway and non-canonical pathway.

Synthesizing miRNA by canonical pathway

RNA polymerase II is responsible for synthesizing long primary miRNA (pri-miRNA) via the canonical pathway, which are subsequently transformed by Microprocessor into precursor miRNA (pre-miRNA). The pre-miRNAs consist of DROSHA, which is a double-stranded RNase III enzyme, and the DGCR8 cofactor (DIGeorge syndrome critical region 8) [10,21]. Exportin 5 (XPO5) then transports these pre-miRNAs to the cytoplasm. DICER1, an RNase III enzyme, cleaves pre-miRNAs in the cytoplasm. The process results in the formation of mature miRNAs which approximately 22 nucleotide mature miRNAs. Following this, the mature miRNA duplex either the 3p or 5p strands is combined with the Argonaute (AGO) family (AGO1-4) in an ATP-dependent manner to create the miRNA-induced silencing complex (miRISC) [22,23] as illustrated in Fig.2.

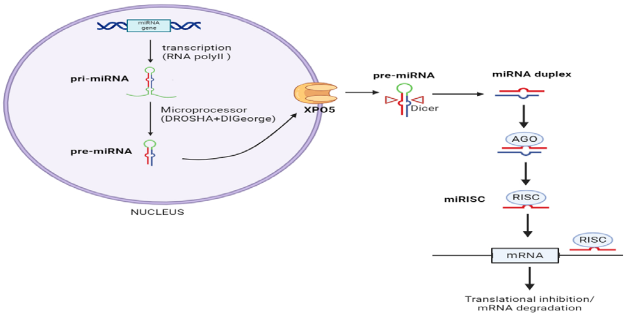

Fig. 2: Overview of canonical miRNA biogenesis pathway. In the nucleus, miRNA gene are transcribed as long pri-miRNAs by RNA polymerase II which are then cleaved by Microprocessor (DROSHA and DiGeorge 8) to produce pre-miRNAs. Pre-miRNAs were then exported to the cytoplasm by XPO5. In the cytoplasm, pre-miRNAs were further processed by DICER to produces mature miRNAs. Mature miRNAs in miRNA-induced silencing complex (miRISC) binds to target mRNA for gene regulation.

Synthesizing miRNA by non-canonical pathway

The non-canonical processing of miRNAs involves the microprocessor complex processing a short hairpin RNA (shRNA), leading to the creation of pre-miRNA. This pre-miRNA is subsequently delivered to the cytoplasm by XPO5. This pathway proceeds through mechanisms that are not dependent on Dicer or Drosha/DGCR8. The pre-miRNA undergoes cleavage by AGO2-dependent enzymes, which do not require Dicer, resulting in the production of mature miRNA in the cytoplasm [24,25].

This will result in the production of a functioning miRISC complex where a single strand of the mature miRNA (the guide strand) is bound to an AGO protein. The guide strand is retained within the miRISC, enabling it to direct the complex towards target mRNAs located at the 3' UTR. This leads to the inhibition of translation, deadenylation, and decapping of the mRNA [26,27]. Additionally, miRNA binding sites have been identified in several regions of mRNA, including the 5' UTR, coding sequence, and promoter regions [27]. Gene expression is suppressed by the binding process [28,29], but the interaction of miRNA with the promoter region can stimulate transcription [30]. It is likely that these pathways interact with each other and regulated differently depending on the type of gene or cell [31].

It is possible to regulate miRNA biosynthesis at various levels, including the promoter level. The transcription of pri-miRNA can be modulated by the stimulation of growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), VEGF, or Wnt signalling [18,32]. Additionally, epigenetic factors such as DNA methylation and histone modifications can also influence miRNA expression and play a crucial role in the expression of miRNA [18].

Regulation of gene expression by miRNA

miRNA modulates gene expression by assessing the level of complementarity between the miRNA and its target gene [18,33]. The level of complementarity between the target mRNA determines whether the target mRNA is sliced by AGO2 or if it undergoes translational inhibition and degradation mediated by miRISC [29,34]. Translational degradation of transcripts is mostly mediated by the binding of miRNA to target mRNA, even when the complementarity between them is imperfect [34]. This imperfect interaction between miRNA and mRNA means that a single miRNA could potentially target more than one mRNA. A high complementary miRNA-mRNA interaction induces participation of the RISC complex and targets mRNA cleavage [17,18,25,35] . Both processes occur in processing body (P-bodies) which are the cytoplasmic foci. The P bodies consist of a high concentration of ribonucleoproteins, mRNA cleavage factors, and miRNAs. These components function as cytoplasmic centers for processing mRNA, assisting in the regulation of untranslated transcripts through silencing, or degradation [17,25,35].

miRNAs dysregulation in cervical cancer development and progression

The carcinogenic potential of cervical cancer results from interactions between viral, host and environmental factors that induce tumor growth, invasion, and metastasis [18]. Several studies have found deregulated miRNA expression profiles between normal and malignant cells in various cancers. Tumorigenesis is driven by changes in the expression of several miRNAs that control the expression of an oncogene or tumour suppressor gene [36].

Evidence indicates that aberrantly expressed miRNAs can function as either tumour suppressors or oncomirs in the development and advancement of cervical cancer. When miRNAs increase the expression of a target tumour suppressor protein, they are defined as oncomirs. Conversely, when they reduce the expression of a particular oncogene, they are referred to as tumour suppressor miRNAs. The novelty of miRNAs is that they can function as tumour suppressors when oncogenes are targeted, and when underexpressed, they can also function as oncomirs when tumour suppressor genes are targeted. Table I demonstrates the involvement of miRNAs in the development and progression of cervical cancer. Certain miRNAs influence carcinogenesis at all stages, while others are only essential during the transition phase as shown in Fig. 3.

Table I: Expression profile of miRNAs involve in cervical cancer

miRNAs	Target Gene	Cellular Process	Refs
Up-regulated			
miR-21	PTEN, RASA1, TIMP3, AP-1,	Tumour progression and metastasis	[65–67]
miR-886-5p	BAX	Cell transformation and progression	[37]
miR-148a	PTEN, P531NP1, TP531NP2	Tumour suppression	[69,70]
miR-10a	HOX genes	Cell transformation and progression	[70]
miR-132			
miR-196a			
miR-106a	LKB1, TIMP2	Cell proliferation and migration	[71,72]
miR-183	ITGB1, MMP9	Cell proliferation and migration	[73,74]
miR-92a	FBXW7, p21, DKK3	Cell proliferation and viability	[75]
Down-regulated			
miR-34a	NOTCH, p181nk, CDK4, CDK6, CyclinA, E2, E2F1, BCL1, BIRC3	P53-dependent pathway (cell cycle progression and cellular senescence)	[76,77]
miR-143	PPAR signalling	Cellular growth and proliferation	[39,40]
miR-203	P63-family	Keratinocyte differentiation / maintenance of HPV episome	[55–57,78]
miR-218	LAMB3, SFMFBT1, DCUN1D1	Focal adhesion, cell migration and invasion	[79]
miR-372	CDK2, Cyclin A1	Cell growth (induced arrest in S/G2 phases)	[80]
miR-145	IGF-1	Cellular movement	[81]
miR-99a miR-513 miR-29a miR-203	IGF-1, BCL2L2, VEGFA, CDK6	Cell death and tissue development	[70]
miR-100	PLK1	Cell growth, cell cycle and apoptosis	[82]
miR-101	Cox-2, JAK2	Cell proliferation, invasion and apoptosis	[83]
miR-138	c-Met, hTERT	Cell proliferation and invasion	[41,42]
miR-23b	six1, ALDH1A1, c-Met, Zeb1	Cell migration and invasion	[84–86]
miR-494	SOCS6, PTEN, HCCR1	Cell proliferation and invasion	[87–89]

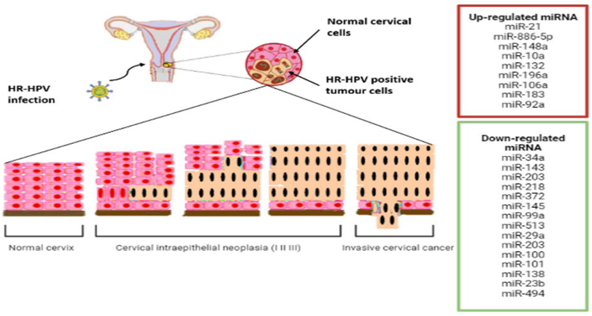

Fig. 3: miRNAs related to HPV-induced cervical cancer carcinogenesis.

Gocze et al., conducted a study which found that the expression of miR-196 was increased during the progression from CIN3 to invasive cervical cancer [35]. The expression levels of miR-26a, miR-29a, miR-99a, miR-143, miR-145, miR-203, and miR-513 showed a significant decrease following the progression to invasive cervical cancer. Conversely, the expression levels of miR-16, miR-27a, miR-106a, miR-142-5p, miR-197, and miR-205 reduced throughout the progression from normal to CIN to invasive cervical cancer [36-38]. Studies has shown that the aberrant progression of pre-cancerous lesions into cancer is promoted by the increased expression of miR-15b, miR-16, miR-21, and miR-21-3p, as well as the decreased expression of miR-218 and miR-376. Furthermore, other study has shown that the levels of miR-195, miR-199b-5p, miR-218, and miR-497 were significantly reduced in cases of CIN2 or CIN3 and invasive cervical cancer [31,37].

miRNAs act as oncomirs in cervical cancer

Several oncomirs have been discovered in cervical cancer. miR-21 is one of the examples of oncomirs that is up-regulated in cervical cancer. miR-21 up-regulation leads to enhance cell proliferation, migration, invasion and survival in many malignancies as well as cervical cancer. In cervical cancer, miR-21 has been demonstrated to decrease the expression of cellular genes, including p53 and Cdc25, which control cell proliferation, as well as RECK and TPM1, which inhibit metastasis. Additionally, miR-21 reduces the levels of PDCD4 and PTEN, which promote apoptosis, in cervical cancer [39,40]. Besides, miR-21 also targets CCL20 which involved in cancer development and metastasis [41]. Inhibition of miR-21 can potentially disrupt the cell cycle and enhance the sensitivity of cancer cells to chemotherapy drugs like cisplatin [39–42]. This indicates that miR-21 may function as an oncogene in human cancer.

Another overexpressed miRNA in cervical cancer is miR-886-5p, which has a role in suppressing the expression of BAX [43]. Cervical cancer has been associated with reduced expression of Bax, which has been associated with a decrease in apoptosis and an increase in proliferation [44]. Furthermore, studies HPV16+H8 cells have indicated that miR886-5P modulates Bax expression through translational inhibition, which is crucial for the development of cervical cancer [43,44].

miRNAs act as tumour suppressor in cervical cancer

miR-143 is a tumour suppressor miRNA targeting kRas, Maccl, and Bcl-2. These proteins are implicated in the ERK5 and MAPK driven signaling pathway [45]. Bcl-2 is an oncogene that functions by suppressing cellular apoptosis, resulting in unregulated cell growth when it is overexpressed. In addition, the excessive expression of Bcl-2 has the potential to lead to the metastasis of cancer cells to other parts of the body. Studies on miR-143 in HeLa cells demonstrated that reducing the level of miR-143 led to an increase in the expression of Bcl-2, whereas increasing the activity of miR-143 resulted in a reduce in Bcl-2 levels [45,46].

Furthermore, miR-138 is a type of microRNA that acts as a tumour suppressor. It plays a crucial role in the regulation of telomerase which is the enzyme associated with cell immortality and carcinogenesis. Specifically, miR-138 helps to extend the length of telomeres at the ends of chromosomes. The activity of telomerase relies on the expression of hTERT, and miR-138 inhibits the expression of hTERT, leading to a reduction in telomerase activity [47,48].

miRNAs associated with HPV infection in cervical cancer

HPV infection is the main risk factor for the development of cervical cancer. The persistence of HR-HPV infection, particularly by HPV16 and 18 subtypes, in combination with other contributing factors can lead to cellular alteration which resulting in a progression from CIN1 to severe neoplasia which is CIN2 or CIN3 and ultimately to invasive cancer. The infection is mainly facilitated by the viral oncoprotein (E5, E6, and E7). The oncoproteins play a role in various cellular processes such as cell transformation, regulation of the cell cycle and growth factor, activation of apoptosis, regulation of endoplasmic reticulum (ER) stress, and evasion of the immune system [31].

Recent studies had proposed that the HPV oncoproteins also regulate the host miRNA profile (see Table II). The HPV oncoproteins were found to be responsible for the change in miRNA expression. Recent studies have suggested that the oncoprotein HPV E6, E7, and E5 may have an involvement in controlling the expression of host miRNA [49,50]. A study comparing the expression of miRNAs in samples of cervical cancer that are positive and negative for HPV revealed that the presence of the HPV oncoprotein has a substantial influence on miRNA expression. The oncoproteins E6 and E7 were found to significantly increase the expression of miR146a, miR-205, and miR-224, whereas decreased the expression of miR-29 [49-51].

Table II: miRNAs that are regulated by HPV oncoproteins

miRNAs	Up-/ Down-regulated	Target Gene	Cellular process	Refs
E5 oncoprotein				
miR-146a	Up-regulated	ZNF813	Cell adhesion and cell cycle	[90,95]
miR-324-5p	Down-regulated	CDH2, CTNNB1	Trans-endothelial migration	[91,92]
miR-203	Down-regulated	p63	Cell migration and motility	[58,60,90]
E6 oncoprotein				
miR-34a	Down-regulated	P18Ink4c, CDK4, CDK6, Cyclin E2	Cell progression and cellular	[53,93]
miR-218	Down-regulated	LAMB3, SFMFBT1, DCUN1D1	Focal adhesion, cell migration and invasion	[79]
miR-23b	Down-regulated	uPA	Cell migration	[88–90]
E7 oncoprotein				
miR-15b	Down-regulated	CCNA2, CCNB1, CCNB2 MSH6, MCM7	Recognition of mismatched nucleotide and initiation of replication	[94]
miR-15a miR-16-1 miR-203	Down-regulated	c-Myc, c-Myb, PPAR	Cell proliferation, survival and invasion	[59,78]
E6/E7 oncoprotein				
miR-29	Down-regulated	YY1, CDK6	Cell progression and apoptosis	[95]

E5 oncoproteins can influence changes of the cell and evasion of the cell to the immune response [18]. In the case of HPV16 infection, the E5 oncoprotein enhances the activation of EGF-R through ligand-dependent mechanisms and stimulates proliferation that is dependent on EGF. This indicates that the oncoproteins preferred membrane localization [51,52]. In addition, E5 oncoprotein interferes with vascular-ATPase (V-ATPase) which enhance the recycling of EFGR thereby reversing the acidification process [53]. In a previous study, HPV16+ keratinocytes expressing E5 showed to able downregulate miR-146a, miR-203 and miR-324-5 [51].

The HPV16 E6 protein has been shown to inhibit the expression of miR-23b, miR-34a, and miR-218, leading to the progression of tumours and metastasis [3]. miR-34a has been identified as a specific transcriptional target of TP53, which acts as a trans-activator for miR-34a. During viral infection, the expression of miR-34a was down regulated, leading to the destabilization of TP53. According to a study conducted by Chang et al, expression of miR-34a is found to be reduced in pre-malignant HPV infection of cervical cancer tissue and cells [54]. These miRNAs target primarily proteins of the cell cycle including CDK4, cyclin E2, E2F-1, MET and Bcl-2 [18,55,56]. Whereas there are also studies that demonstrated participation of miR-34a on Notch-1 signaling pathway. The inhibition of TP53 activity and the inhibition of miR34a activity interfere with the multi-step regulation of the cellular cycle, leading to a reduction in cellular senescence and an elevation in apoptosis. This alteration in cell division and proliferation results in cell transformation in the cancer cell [57].

This HR-HPV E7 oncoprotein has shown to target many tumour suppressor miRNAs like miR-15a, miR-15b, mirR-16 and miR-203 [3,4]. miR-203 is essential for regulation of the keratinocytes transition from a proliferative state in undifferentiated basal cells to a non-proliferative state. Additionally, it has been demonstrated to promote the maturation of epithelial cells [58]. A decrease expression of miR-203, therefore critical role in aiding the active phase of the HPV life cycle in the differentiation of epithelial cells. miR-203 targets the p63 transcription factor, which is responsible for maintaining the equilibrium between epithelial proliferation and differentiation [59]. Studies has indicated that miR-203 is regulated through mitogen-activated protein (MAP) kinase/protein kinase C (PKC) pathway [58,59]. While, in several studies, miR-203 showed their down-regulation by E7 could retain tumour cell's characteristics [60,61].

The tumour suppressor miRNAs miR-15a and miR-16 can influence cell proliferation, survival and invasion. Studies has showed the overexpression of the miR-15a and miR-16 in cervical cancer cells [61,62]. In order to associate the involvement of the miRNAs with HPV infection, a comparative study was conducted. The study specifically examined the expression levels of miR-16 in raft tissues produced from human foreskin keratinocytes, both with and without HPV18 infection. The study found that when cells expressing HPV18 E6 and E7 were infected with retroviruses, the expression of miR-16 was exclusively elevated in tissues that expressed the HPV E7 protein, while tissues expressing HPV E6 did not show such an increase. This showed that E7 is responsible for the elevated expression of miR-16 [44].

CONCLUSION

miRNAs have revealed their important role in biological pathways involved in cervical cancer development and progression. Given the considerable time lag between epithelial atypia and invasive cervical cancer, there is excellent potential of these miRNAs to be used as biomarker, however, details interaction between those miRNAs with specific signaling pathway that may involve is still unclear. This review has elucidated how specific miRNAs are involved in the regulation of key oncogenes and tumor suppressor genes, contributing to the progression and malignancy of cervical cancer. By understanding the stage wise alterations of miRNAs and their molecular pathway involved in the development of cervical cancer and discovery of new biomarkers for early detection, prognosis, and therapeutic targets in HPV-associated cervical cancer. The insights gained from the review pave the way for the development of miRNA-based diagnostic tools and treatments, which could significantly improve patient outcomes and open up new pathways for personalized medicine in cervical cancer.

ACKNOWLEDGMENT

We would like to acknowledge MOHE for FRGS grant (FRGS/1/2020/SKK0/USM/02/30) and School of Medical Sciences, USM Health Campus, Kubang Kerian Kelantan Malaysia for the support.

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