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miRNA as viral transcription tuners in HPV-mediated cervical carcinogenesis

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1. ABSTRACT

High-risk human papillomaviruses (HPVs) are oncogenic DNA viruses that promote carcinogenic signaling by their oncoproteins mainly E6 and E7. A well-defined promoter regulates expression and enhancer region on HPV genome containing number of *cis* elements that essentially require a set of cognate host transcription factors to regulate viral promoter gene activity. Expression of these host factors is tightly regulated at multiple levels such as transcriptional, post-transcriptional and post-translational level. Discovery of microRNAs (miRs) in recent years and differential expression of a set of specific miRs in HPV infection and cervical lesions indicate that among various regulatory mechanisms, role of these differentially expressed miRs in the post-transcriptional control is pivotal. Present review analyses and attempts to compile currently available miR data related to HPV infection and cervical carcinogenesis with a special focus on miRs that may regulate expression of the host and viral factors particularly responsible for viral transcription leading to carcinogenic progression of the lesion. Further, the review attempts to assess the therapeutic potential of miR-based strategies in therapeutic targeting of HPV infection during cervical carcinogenesis.

2. INTRODUCTION

Cervical cancer is the second most commonly diagnosed cancer and the third leading cause of cancer death in women worldwide. An estimated 527,600 new cervical cancer cases and 265,700 deaths were reported worldwide in 2012. More than 90% of disease burden is contributed by the developing countries. India accounted for 25% of cervical cancer deaths (67,500) (1). It is a well-established fact that HPV infection is the primary etiological agent of cervical cancer (2–4) but with no specific clinically-available treatment for HPV infection (5). To date, over 110 different HPV types have been identified, and about 30 of these infect epithelial cells of the genital tract (6). Papillomaviruses exhibit a high degree of specific cellular tropism for squamous epithelial cells of different organ sites (7) and have been associated with various clinical manifestations ranging from benign hyperplastic

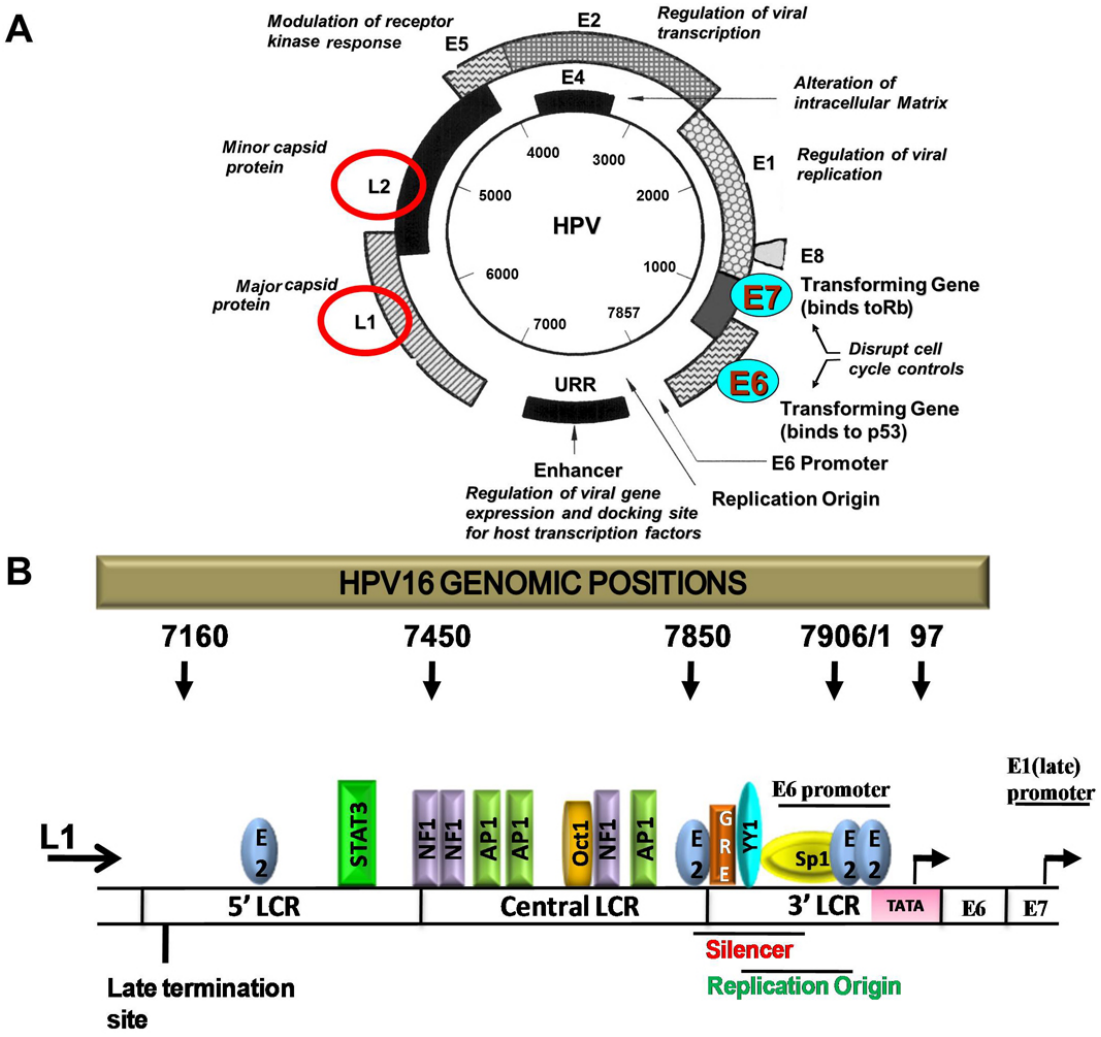

Figure 1. A. HPV16 genomic organization and functions of viral gene products. **B.** Schematic presentation of viral URR with potential host transcription factor binding sites.

epithelial proliferative innocuous lesions (warts, papillomas) to cancer. These proliferative hyperplastic lesions can be cutaneous (skin warts) or can involve mucosal squamous epithelium of oral, pharynx, the esophagus or of the genital tract. On the basis of their association with disease types, papillomaviruses are classified into high-risk (HR) and low-risk (LR) types. HR HPV types are often associated with carcinoma of ano-genital tract, whereas the LR HPV types are associated with low grade benign lesions, like skin/ genital warts and condylomata acuminate and rarely associated with malignancy. Till now, 12 HR HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) and 8 intermediate or probable HR HPV types (HPV 26, 53, 66, 67, 68, 70, 73 and 82) (8) have been described which collectively contribute to overall HPV-attributable cancer burden worldwide. Among them, HPV16 and HPV18 are the most prevalent genotypes. Together, they are responsible for more than 80% of global HPV-associated cancerous lesions. The link between genital HPV infections and cervical cancer was first demonstrated in the early 1980s by Harald zur Hausen and his co-workers (9, 10). Since then, a number of epidemiological and functional studies have unraveled the causal link between high-risk HPV infection and cervical squamous cell carcinoma (11).

Among 6 early proteins (E1, E2, E4, E5, E6, and E7) that are encoded by HR-HPVs specifically the E6 and E7 play a pivotal role in carcinogenic progression (Figure 1A). Expression of these proteins is tightly regulated by one of the two promoters (Early and Late) that control spatio-temporal expression of HPV genomes in different mucosal linings (12). This non-coding viral promoter along with enhancer region is termed synonymously as Long Control Region (LCR) or Upstream Regulatory Region (URR). The URR contains a number of *cis* elements that essentially requires a set of host transcription factors to regulate viral promoter activity (13) (Figure 1B). Therefore,

availability of the host factors directly governs and orchestrates viral gene expression and downstream pathogenic events. Expression of these host factors is tightly regulated at multiple levels such as transcriptional, post-transcriptional and post-translational level. Since the discovery that small RNA that can act as a specific regulator of gene expression (14), RNAs are emerging as intense area of research. MicroRNAs (miRs/miRNAs) are a family of highly conserved short non-coding RNAs involved in post-transcriptional gene silencing. Over 2500 human miRNAs have been recorded in miRBase (www.mirBase.org). miRs have been found in a variety of organisms from viruses to humans (15, 16). miRs target multiple mRNAs involved in variety of cellular responses or signaling pathways by promoting their degradation or translational silencing and thus act as negative regulators and fine tuners of the biological response.

Recent studies show role of miRs in oncogenesis (17). However, depending upon the function of the gene product of miR target(s), the end result of any miR's action could be tumor promoting or tumor suppressive. In humans, the majority of miRs (70%) are transcribed from introns and/or exons, and approximately 30% are located in intergenic regions (15). Apart from the host miRs recent study has identified and validated papillomavirus-encoded miRNAs in human cervical lesions and cell lines for the first time. Interestingly, two miRs were found to be encoded by HPV16, one by HPV38 and one by HPV68 (18), however, their functions and downstream pathological effects are yet to be elucidated. These observations, in view of carcinogenic role of HPV, therefore, indicate strong interplay between host and viral miRs not only in regulation of target host transcripts whose gene products are relevant to cancer development and progression but also in regulation of viral transcripts through targeting host transcription factors that control expression of viral oncogenes. Various efforts have been made in the past decade to improve our understanding of the altered miR expression by oncogenic HPV infection that may have important contribution in development of cervical cancer. However, how alterations in specific miRs translate into control of viral genome is poorly defined. Present review assesses currently available miR data related to HPV infection and cervical carcinogenesis with a particular focus on miRs that regulate expression of host and viral factors, which control viral transcription and examines the strength and bottlenecks in developing miR-based prognostic and therapeutic strategies for control of HPV infection and cervical carcinogenesis.

3. REGULATION OF VIRAL ONCOGENE EXPRESSION BY URR

On HPV genome, a transcriptional control region designated as URR separates viral late and early genes. This region is approximately 800–1000bp (covering about 10% viral genome). It does not encode any protein, but contains the origin of replication, viral early promoter and enhancer sequences that play regulatory role in HPV-associated cell transformation and viral life cycle (Figure 1B). All papillomavirus URRs studied so far contain epithelial specific constitutive enhancers (19) that contribute to the epithelial tissue tropism of HPVs and control of E6/E7 transcription. Most HPV types have a promoter in front of the E6 gene in common (20, 21). Functionally, the 850bp HPV16 URR can be divided into three parts: 1) A 5'-terminal portion of unknown function; 2) A central 400bp constitutive enhancer essential for E6/E7 promoter activity; 3) A promoter proximal region containing E6/E7 promoter p97 at its 3' end. Because of its potential for binding with a wide array of specific host transcription factors, URR works as a primary interface between host and the virus and thus determines the compatibility of specific types of HPVs to the host tissues resulting in productive infection (22). One or more host cell transcription factor binding sites and other keratinocytes-specific enhancers for AP-1, Sp1, NF-1, TEF-1, TEF-2, Oct-1, AP-2, KRF-1, YY1, NF-κB, STAT3 and glucocorticoid responsive elements have been identified in the URR region of HPV16 and other HPV types (23–32). Interestingly, many of the factors/cognate binding sites such as that of AP-1 are indispensable for expression of viral oncogenes. Any nucleotide change resulting in reduced bindings of these transcription factors to their binding site on HPV URR, or alteration in the expression or activity of the transcription factor may adversely affect transcription of the viral oncogenes. Moreover, aberrant expression and constitutive activation of many of these factors like AP-1, NF-κB, and STAT3 have been demonstrated in cervical cancer (33, 34). These transcription factors are known to have independent carcinogenic risks as they induce and promote carcinogenic inflammation (35, 36). Therefore, the factors that control the expression and/or activity of these transcription factors during HPV infection need further investigation. Identification of miR-mediated post-transcriptional control has opened up several investigations that might answer some of these issues and may lead to better understanding of transcriptional control of HPV.

4. MICRORNAS IN CARCINOGENESIS

miRs, short RNA molecules of 19–25 nucleotides in length, play a key role in regulating gene expression by controlling the level of transcripts available for translation by triggering degradation of their target mRNAs (37). miR genes are generally transcribed by RNA polymerase II (Pol II) in the nucleus and are exported to the cytoplasm as mature miRs. A schematic presentation of miRs biogenesis is given in Figure 2. The mature miRNA binds to complementary sites in the mRNA target to negatively regulate

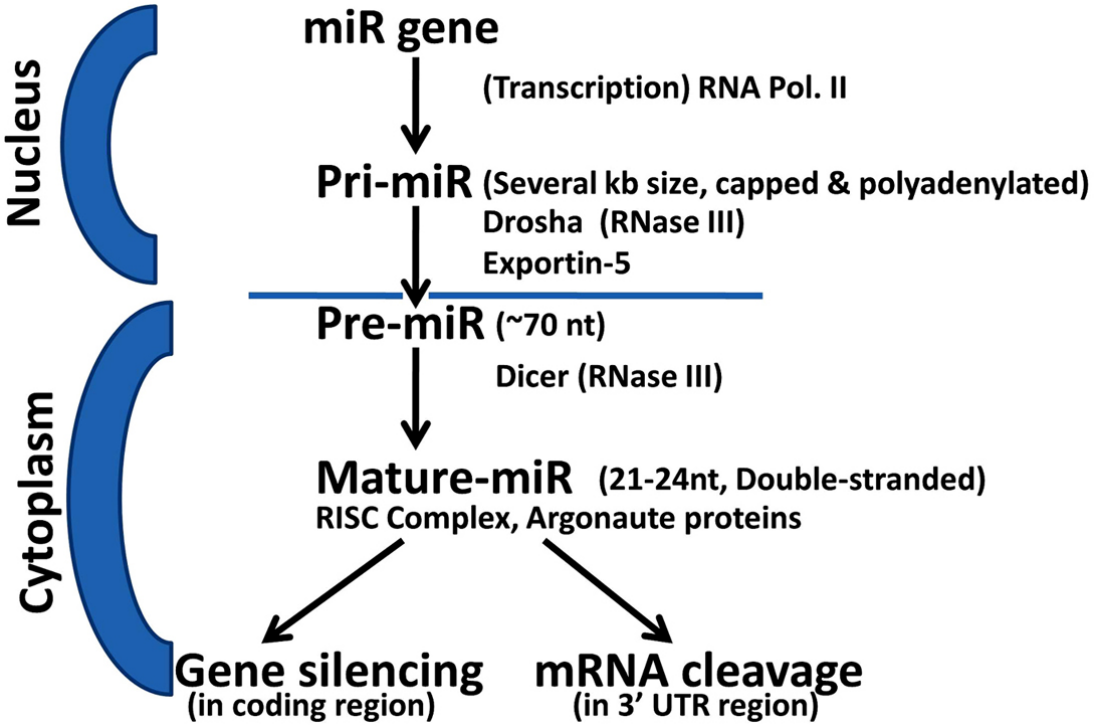

Figure 2. Brief outline of biogenesis of functional miRNAs. miRNA genes are generally transcribed by RNA Polymerase II (Pol II) in the nucleus to form large pri-miRNA transcripts which are several kilobases in size, capped and poly adenylated. These pri-miRNA transcripts are processed by the RNase III enzyme Drosha and its co-factor, Pasha, to release the ~70-nucleotide pre-miRNA precursor product. RAN–GTP and exportin-5 transport the pre-miRNA from nucleus into the cytoplasm. RNase III enzyme, Dicer, processes the pre-miRNA to generate a transient ~22- nucleotide miRNA:miRNA* duplex. This duplex is then loaded into the miRNA-associated multiprotein RNA-induced silencing complex (miRISC), which includes the Argonaute proteins, and the mature single-stranded miRNA is retained in this complex. The mature miRNA then binds to complementary sites in the mRNA target to negatively regulate the gene expression. The miR negative action mechanism is one of two ways that depends on the degree of complementarity between the miRNA and its target mRNA. miRNAs that bind to the 3′ untranslated regions of their target mRNA genes with imperfect complementarity block target gene expression at the level of protein translation. miRNAs that bind in the coding sequence or open reading frame of their mRNA target with perfect (or nearly perfect) complementarity induce target-mRNA cleavage. Adapted with permission from (49).

corresponding gene expression. The miR negative regulatory action is executed in one of the two ways that primarily depends on the degree of complementarity between the miRNA and its target mRNA. miRNAs that bind to the 3′ UTR of their target mRNA genes with imperfect complementarity block target gene expression at the level of protein translation. miRNAs that bind in the coding sequence or open reading frame of their mRNA target with perfect (or nearly perfect) complementarity induce target-mRNA cleavage. miRs are important players in regulation of various biological processes including cell differentiation, proliferation and apoptosis (38–43). Expression of miRNAs is altered in a number of human diseases from psychiatric disorders (44) to cancer (45). Extensive research shows that miRs play an important role in cell apoptosis (46), suppression of tumor growth, invasion and metastasis in HPV-positive cancer (47). Because of being an upstream regulatory molecule with multiple targets, the changes in levels of miR expression are anticipated to be the cause of multiple dynamic alterations seen in mRNA and protein profiles during carcinogenesis. Studies have revealed that miRNAs frequently reside within fragile sites, are often involved in cancer development (48). However, it has remained a puzzle whether altered miR expression is a cause or consequence of carcinogenic processes. Emerging data shows appearance of alterations in a limited set of specific miRs in many cancer types indicate to a potential regulatory role of these miRs in carcinogenic process and could be a reflection of dynamic state of expression of tumor suppressors and oncogenic oncomiRs.

5. ALTERED MIR EXPRESSIONS IN CERVICAL CANCER

Recent advances in the field of miRNA resulted in exploration of these small regulators in cervical cancers also. Studies describing alterations in the miRs profile in cervical cancer has been recently reviewed in detail (50, 51) and the subject is beyond the focus of present article. However, some of the salient studies have been compiled in Table 1 to assess the commonalities and differences in differential miR profiles reported (52–59). Interestingly, leaving a few miRs each study demonstrated a different set of miR that are differentially expressed in cervix cancer thus making the overall manifestation of miRs in this disease

Table 1. Different miRNAs found altered during cervical carcinogenesis

miRNAs	Expression Change	Sample Type	Technique	Refernces
miR-21	Upregulation	Cervical cancer cell lines and tissues	miRNA cloning	(52)
Let-7a, Let-7b, Let-7c, , miR-23b**, miR-143**, miR-196b	Downregulation	Cervical cancer cell lines and tissues	miRNA cloning	(52)
miR-9, miR-127, miR-133a, miR-133b, ***miR-145***, miR-199-s, miR-199a*, ***miR-199a***, miR-199b, and miR-214	Upregulation	Cervical tissues	Taqman real time quantitative PCR	(53)
miR-149 and **miR-203**	Downregulation	Cervical tissues	Taqman real time quantitative PCR	(53)
miR-182, **miR-183** and miR-210	Upregulation	Cervical cancer cell lines	Microarray	(54)
miR-126, **miR-143**, ***miR-145***, miR-195 and miR-218	Downregulation			
miR-21, **miR-24**, miR-27a, and miR-205	Upregulation	Cervical cancer cell lines	miRNA cloning	(55)
miR-143 and **miR-145**	Downregulation			
miR-15b, miR-16, miR-155 and miR-223	Upregulation	Cervical tissues	Microarray	(58)
miR-126 and miR-424	Downregulation			
miR-9, miR-10a, miR-10b, **miR-24**, miR-146b,miR-181a, **miR-183**, miR-193b, miR-200a , and miR-204	Upregulation	Cervical tissues	Microarray	(56)
miR-10a, miR-132, miR-148a, miR-196a, and miR-302b	Upregulation	Cervical tissues	Microarray	(57)
miR-26a, miR-29a, miR-99a,**miR-143**, **miR-145**, **miR-*199a*, miR-203** and miR-513	Downregulation	Cervical tissues	Microarray	(57)
miR-21	Upregulation	Cervical cancer cell lines and tissues	PCR	(59)(60)
Let-7a	Downregulation	Cervical cancer cell lines and tissues	PCR	(59)(60)

[1]Bold font indicates miRs reported to be altered in ≥2 studies, Italics with contrasting reports

more complex. For example, our recent study (59, 60) and others showed that miR-21 is overexpressed and expression of Let-7a, miR-143, Let-7c, miR-196b, miR-23b and Let-7b is downregulated in cervix tissue biopsies (52). On the other hand, Lee *et al*. demonstrated upregulation of miR-199 and miR-9 and downregualtion of miR-149 and miR-203 in cervical cancer. Similarly, high expression of miR-182 and miR-183 and low expression of miR-126 and miR-143 was reported in another study (54). miR-15b and miR-16 were overexpressed in cervical cancer while reduced expression of miR-126 and miR-143 was observed (55). Similarly, miR-148a and miR-302b were shown to be overexpressed and miR-203 and miR-513 to be downregulated in cervical cancer (57). As of present, studies are focusing to identify the set of miRNAs that can be used as molecular markers in cervical cancer patients (61). These studies defining specific variations in miR profile not only reflect population-specific variation but also indicate dynamic nature of miRs in progressive lesions, which needs a deeper understanding.

It is likely that abundance of any particular miR may vary with respect to the stage of the disease, type of HPV infection, level of expression of viral oncogenes apart from the differences in technology applied and the type of specimen used. Nevertheless, a few miRs were more frequently reported than others, which included miR-9, miR-21, miR-24, and miR-183 that were found overexpressed. On the other hand, let-7a, miR-203, miR-143, and miR-203 were undetectable or under-expressed in cervical cancer tissues and cell lines. Further, a few studies have reported a contrasting profile of some of miRs, particularly miR-145 and miR-199a (53, 54, 57). Assessment of clinical specimen revealed clinical stage and histopathological grade-specific alterations in miR profile (51, 58, 62). Upregulation of specific miRs, miR-200a and miR-9 could predict patient survival (56). Loss of a few miRs (let-7c, miR-10b, miR-100, miR-125b, miR-143, miR-145 and miR-199a-5p) is specifically associated with advanced stage cancer lesions (63). Patients with loss of miR-100 and miR-125b had a greater tendency to show poor prognosis. Some of these reported miRs demonstrate direct or indirect link of altered miR profile with HPV-transcription related factors, which will be discussed in the following sections.

6. HPV INFECTION-ASSOCIATED CHANGES IN HOST MIR PROFILE

Viruses play a major role in regulating host gene expression in many viral infections and a part of these responses are mediated/affected through miRs (64, 65). In case of HPV infection, expression of viral

Table 2. Representative studies showing HPV infection-induced alterations in host miRNA profile

HPV gene	miRNAs	miRNA target	Effect	Sample type	References
HPV16 E6	miR-218↓	LAMB-3↑	Downregulation of miR-218 by E6 and overexpression of LAMB-3 may promote viral infection	Cervical cancer	(54)
	miR-34a↓	E2F↑, p18Ink4c↑	Expression of HR-HPV oncoprotein E6 reduces miR-34a expression by destabilizing p53& promoting cell proliferation	Cervical cancer	(55, 71)
	miR-23b↓	uPA↑	E6 downregulate miR-23b by targeting p53	Cervical cancer	(68)
	miR-145↓	IRS-1↑	Inhibition of p53 -dependent miR-145 up-regulation	Cervical cancer cell lines	(72)
	miR-92↑	PTEN↓	E6 upregulated miR-92 expression, promoted cell growth and invasion	Cervical cancer & cell lines	(74)
	miR-9↑	ALCAM↓, FSTL1↓	Effects independent of p53, regulation of cancer metastasis	Cervical cancer	(75)
	Let-7a↓, miR-21↑	STAT3↑ PTEN↓, MMP-9↑, TIMP↓	Upregulation of STAT3 expression, persistent STAT3 activity due to loss of PTEN	Cervical cancer cell lines	(59)
HPV E7	miR-203↓	p63↑	E7 blocks miR-203 upregulation through MAP kinase pathway	Normal Keratinocytes	(67)
HPV E6/ E7	miR-363↑, (miR-181a, 218, 29a)↓	TS P57↓ P85/CDC42↑	Cell cycle disruption, Negative regulators of p53	HPV16+ & HPV-SCCHN cell lines, human foreskin keratinocytes	(70)
	miR-95↑, (miR-23b, 100, 137, 149, 432, 601, 1202)↓	SNX1↓, (uPA, PTEN, Hes1, FGFR3, MMP13, Plk1LSD1, Cdc42, CtBP1, Akt1 and E2F1,b-Myb, GSK3a, NF-kB)↓	Effects at least in part, due to reduction in the levels of transcription factor p53 by E6 and the release of E2F from the pRb-E2F complex	Transfected human foreskin keratinocytes	(73)
	(miR-24, 205)↓	p27	miR-205 expression is dependent on pRb, target CDK inhibitor p27	Human foreskin keratinocytes	(76)
	IC(miR-17,186,378, 637, 7) ↑ IC(miR-143, 23a, miR-23b, 27b) ↓ E(let-7d, miR-20a, 378a,423, 7, miR-92a) ↑ E(miR-21) ↓	P21↓	Effects independent of p53, intracellular miR-17~92 cluster downregulates antiproliferative p21	Cervical cancer cell lines	(77)
HPV16 E5	miR-146a↑	↓p38, ERK1/2↓	Suppress differentiation of epithelial cells, attenuated immune response in HPV infections	Cervical cancer	(69)
	miR-324–5p↓	N-cadherin ↑, E-cadherin ↑	HPV E5 oncogene may repress miR-324–5p expression in cervical epithelial cells		(69)
	miR-203↓	p63↑, STAT1↑	E5 acts by suppressing differentiation of epithelial cells through downregulation of miR-203 with subsequent upregulation of p63.		(69)
HR HPV	miR-218↓	Not known	miR-218 involvement in pathogenesis	Cervical cancer	(64)
	miR-100↓	PLK1↑	Independent of HPV E6/E7 expression	Cervical cancer and cell lines	(144)

E-Exosomal; IC-Intracellular

oncoproteins especially E5, and E6 are specifically linked with a number of miR alterations and the list is expanding with increasing knowledge of miR-based regulation in HPV infection and cervical cancer (Table 2) (54, 55, 58, 59, 66–77). Recently, Honegger *et al.* showed that HPV E6/E7 silencing significantly alters multiple miRs which contribute to HPV E6/E7-dependent growth of HPV-positive HeLa cells (77). In another study, E5 was found to induce expression of miR-146a, whereas it repressed miR-324–5p and miR-203. These miR alterations were accompanied by suppressed differentiation and attenuated immune response to HPV infections in cervical epithelial cells (69). Similarly, the expression of the HPV16 E6 specifically reduced miR-218 expression, and conversely the expression of epithelial-cell specific

marker LAMB3, a target of miR-218, was found upregulated (54). Other HR-HPVs were later described to downregulate miR-218 expression (66). Expression of E6 was also found associated with reduction of miR-34a expression in organotypic tissues derived from HPV-containing primary human keratinocytes. Reduction of miR-34a expression was attributed to the expression of viral E6, which destabilizes the tumor suppressor p53, a known miR-34a transactivator (78). In addition, E6 oncoprotein decreases the expression of miR-23b that culminates in upregulated expression of its target gene uPA, an inducer of cell migration (68). These studies, therefore, indicate an important role of HPV oncoproteins in alteration of host miRNA profile and this altered miRNA expression profile by itself becomes a major pool of regulators that destabilizes cell growth and survival mechanisms causing events leading to cervical carcinogenesis.

There could be 6 different and independent mechanisms by which HPV affects host miR profile and consequently the host transcriptome. 1). by targeting fragile sites that are often the site of HPV integration (79). About 50% of miR genes are found located at the fragile sites and genomic regions with frequently dys-regulated expression in cancer (48). 2). HPV-mediated epigenetic changes in miR expression (reviewed in (80)). miRs are transcribed as a unit or in groups of 2–19 and can reside in the introns or exons of coding genes or in intergenic regions, the later has its own promoter which allows them to be individually transcribed and hence subject them to epigenetic regulation. 3). Expression of its own miRs (18). Recent study performed using deep sequencing showed at least 2 miRs are encoded by HPV16 and one each by HPV38 and HPV68 (18, 81). These viral miRs are capable of targeting both viral as well as host transcripts. 4). Indirect effect of action of viral oncoproteins E5, E6 and E7. This is among the most widely studied mechanisms by which HPV infection influences host miR profile. E5 was found to induce expression of miR-146a, whereas it repressed miR-324–5p and miR-203. These miR alterations were accompanied by suppressed differentiation and attenuated immune response to HPV infections in cervical epithelial cells (69). Similarly, the expression of the HPV16 E6 specifically reduced miR-218 expression, and conversely the expression of epithelial-cell specific marker LAMB3, a target of miR-218, was found upregulated (54). HR-HPV infections in general were later described to downregulate miR-218 expression (66). Expression of E6 was also found associated with reduction of miR-34a expression in organotypic tissues derived from HPV-containing primary human keratinocytes. Reduction of miR-34a expression was attributed to the expression of viral E6, which destabilizes the tumor suppressor p53, a known miR-34a transactivator (78). In addition, E6 oncoprotein decreases the expression of miR-23b that culminates in upregulated expression of its target gene uPA, an inducer of cell migration (68). Apart from these p53-dependent alterations, HPV has been described to induce p53 independent changes in host cell miR profile (75, 77). 5). Global changes in miR profiles due to changes in miR processing enzyme Drosha (82) which is reported to be overexpressed in cervical cancer (83). 6). Changes in exosomal packaging of miRs. Recent study showed a characteristic shift in the miR signatures of exosomal and intracellular miR profiles following ectopic expression of HPV oncogenes E6 and E7 irrespective of the HR-HPV type (77). These studies, therefore, indicate an important role of HPV oncoproteins in alteration of host miRNA profile and this altered miRNA expression profile by itself becomes a major pool of regulators that destabilizes cell growth and survival mechanisms causing events leading to cervical carcinogenesis and at the same time promote a milieu which is more conducive to viral oncogene expression.

7. MIRS AS UPSTREAM REGULATORS AND DOWNSTREAM TARGETS OF CELLULAR TRANSCRIPTION FACTORS ASSOCIATED WITH VIRAL TRANSCRIPTION

Because of the potential for binding with a set of specific host transcription factors, URR works as a primary interface between host and the virus and thus determines the compatibility of specific types of HPVs to the host tissues resulting in productive infection (22). One or more host cell transcription factor binding sites and other keratinocytes-specific enhancers for AP-1, Sp1, NF-1, TEF-1, TEF-2, Oct-1, AP-2, KRF-1, YY1, STAT3 and glucocorticoid responsive elements have been identified in the URR of particularly HPV16 (23–31). Some important upstream regulators and downstream targets of these transcription factors that control HPV16 URR are depicted in Figure 3. It is important to note that various levels of functional complexities are present among these transcription factors. Some of these transcription factors are basal (such as SP-1, and Oct-1) as they are constitutively expressed and active in all cell types whereas others are inducible (such as AP-1, NF-κB and STAT3). The differential transcriptional outcome occurs if different members of the same family interact (such as AP-1, NF-κB and STAT3). Further, their activity is controlled by multiple regulatory mechanisms (such as phosphorylation) that also include negative feedback mechanisms and involvement of miRs. Listing all possible miR interactions will be quite complex and not relevant to the context. Therefore, only most relevant miRs that have been reported to control the expression of these HPV-related transcription factors and if they have been found altered in cervical cancer have been outlined in Table 3 and some more relevant ones have been discussed below:

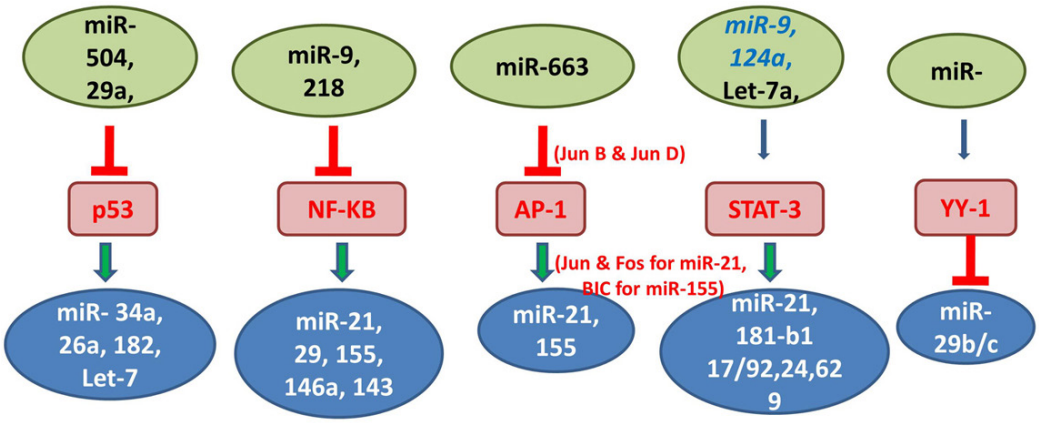

Figure 3. Upstream regulators and downstream target miRNAs of some of the transcription factors that control HPV16 URR.

7.1. Activator protein-1 (AP-1)

Early studies on transcriptional control of HPV oncogenes revealed indispensable role of two AP-1 sites driving the expression of virus-encoded E6 and E7 oncoproteins in HPV16 URR (30, 31, 84, 85). AP-1 is a family of transcription factors containing seven members, c-Jun, JunB and JunD in the Jun family and c-Fos, FosB, Fra-1 and Fra-2 in the Fos family. These members can form homodimers or heterodimers within the same family members or with members of other family (86). Mutational inactivation of AP-1 binding sites in the natural context of the HPV16 URR leads to an almost complete loss of the transcriptional activity of the E6/E7 promoter (87). AP-1 has been shown to develop carcinogenesis in a variety of tissues (88). Our group demonstrated a significant overexpression of constitutively active AP-1 family members in cervical precancer and cancer tissues (33). Recently, miR-7B has been shown to decrease the translation efficiency of the unstable c-Fos mRNA (89). miR-663 decreases AP-1 activity and impairs its upregulation via lipopolysaccharides by directly targeting JunB and JunD transcripts (66). Also, AP-1 binding site has been revealed in miR-21 promoter (90).

7.2. Nuclear factor kappa B (NF-κB)

The role of NF-κB, a transcriptional regulator, in linking inflammation and tumorigenesis has been supported by accumulating evidences (91, 92). NF-κB is constitutively activated during human cervical cancer progression (93). HPV16 E6 and E7 proteins modulate the expression and the sub-cellular localization of NF-κB precursors (94). Also the HPV16 E5 expression leads to NF-κB activation, in part, with AP-1 in cervical carcinogenesis (95). Two putative NF-κB binding sites are reported in the miR-155 promoter (96). A positive correlation between miR-155 upregulation and NF-κB activation has been shown by some studies (78, 97–100). NF-κB activation is increased on binding of miR-181b-1 in the promoter regions of STAT3. The increased transcription of miR-181b-1 inhibits CYLD, negative regulator of NF-κB (101), which in turn causes increased NF-κB activation in MCF-10A cells. miR-21 works within the inflammation-transformation positive feedback loop through STAT3-mediated regulatory circuits, which down-regulate PTEN expression to increase NF-κB activity (36). miR-301 activates NF-κB in a positive feedback loop in which miR-301a represses Nkrf to elevate NF-κB activity and NF-κB promotes the transcription of miR-301a (102). NF-κB binds to a site upstream of the let-7 RNA coding region. NF-κB activation and subsequent repression of let-7 result in high levels of IL-6. These high levels of IL-6 are required for sufficient binding to the IL-6 receptor to cause activation and nuclear entry of the STAT3, which then activates VEGF (35).

7.3. Signal transducers and activators of transcription-3 (STAT3)

Recent studies show involvement of STAT3 in cervical carcinogenesis. STAT proteins comprise a family of transcription factors latent in the cytoplasm that participate in normal cellular events, such as differentiation, proliferation, cell survival, apoptosis, and angiogenesis following cytokine, growth factor, and hormone signaling (103). Overexpression of STAT3, one of the important member of the STAT family, has been observed in a wide number of human cancer cell lines and primary tumors including blood malignancies, solid neoplasia (104, 105) and cervical cancer (34, 59, 60, 106). Current literature indicates a strong interaction of STAT3 signaling with HPV infection during cervical carcinogenesis. STAT3 activation may serve as an important player in HPV-mediated cell cycle dysregulation. Upregulated STAT3 expression is expected to repress the *de novo* production of p53, whereas E6 mediates the degradation of already produced p53 proteins thereby critically depleting the cellular p53. STAT3 binding

Table 3. Cellular transcription factors associated with viral transcription and respective miRs that regulate their expression/activity

Transcription Factor (145)	Regulation	TF Status in CaCx	Subunits	Corresponding Validated Regulatory miR (From Pubmed/ miR database)	Status of Respective miR in Cervical Cancer (R)
AP-1 5'-TGACTCA-3' (86)	Induced	Constitutively active with overexpression of c-Fos and JunB (33)	c-Jun	miR-21 (146, 147), miR-23 (148), miR-155 (96), miR-206 (149)	miR-21↑ (60), miR-23↑ (77) , miR-155 ↑ (150), miR-206↓ (151) miR-92a ↑ (152)
			c-Fos	miR-21 (146), miR-23 (148), miR-92a (153)	
			JunB	miR-21 (146)	
SP-1 5′-(G/T)GGGCGG(G/A) (G/A)(C/T)-3′ (154)	Basal	Plays an important role for the activation of the E6/E7-promoter (155)		miR-22 (156), miR-27a (157), miR-29b (158, 159), miR-34c (160), miR-17–92 cluster (161), miR-132 (162), miR-133a, miR-133b and miR-145 (163, 164), miR-141 and miR-146b-5p (165), miR-149 (166), miR-182 (167), miR-183 (168), miR-200 and miR-200b (169–171), miR-335 (172), miR-375 (173), miR-1188 (174), miR-3151 (175)	miR-27a ↑ (176), miR-34c ↓ (177), miR-17–92 cluster ↑ (178), miR-132 ↓ (179), miR-145 ↓ (180), miR-182↑ (181), miR-183↓ (182)
NF-1 5'-TTGGC-3' (25)	Basal	NF-1 binds only poorly to recognition sites within URRs and only marginally contributes to transcriptional activation (155)	NF1A	miR-217 (183), miR-223 (184)	miR-223↓ (185), miR-124↓ (186)
			NF1B	miR-124 (187), miR-136 (188)	
TEF-1 5'-GTGGAATGT-3' (189)	Basal	Active in human keratinocytes and essential for HPV16 transcription (190)		No report	No report
Oct-1 5'-ATTTGCAT-3' (191)	Basal	High expression (192)		miR-1467, miR-1185, miR-4493 and miR-3919 (192)	miR-1467, miR-1185, miR-4493 and miR-3919 (192)
AP-2 5'-GCCN3GGC-3' (193)	Induced	Transcriptional control of HPV (194)	AP-2α AP-2β AP-2γ AP-2δ AP-2ε	No report	No report
KRF-1 5'-TAACTATATCC-3' (29)	Basal	Binding is necessary for high level of transcriptional activation of HPV18 (29)		No report	No report
YY-1 5'-GCCGCCATTTTG-3' (195)	Basal	Overexpressed and positive correlation with HPV E6/E7 (58), Negative regulation of HPV transcription (122, 145)		miR-7 (196), miR-193a-5p (197), miR-206 (149),	miR-7 ↓(198), miR-206 ↓(151)
STAT-3 5'-TT(N)4–6AA-3' (199)	Induced	Constitutively active with overexpression of STAT3 (34)		Let-7a (109), miR-7 (200), miR-17–92 cluster (201), miR-98 (202), miR-106b (173), miR-30c (203), miR-130b (204), miR-181b-1 (205), miR-221 & miR-222 (194), miR-874 (206), miR-1181 (207)	Let-7a ↓ (59, 60),
NF-κB 5'-GGGRNYY YCC-3' (208) (in which R is a purine, Y is a pyrimidine, and N is any nucleotide)	Induced	Constitutively active with overexpression of p50 homodimers (33)	P50	miR-21 and miR-34ac (209), miR-155 (96), miR-183, miR-218 (210), miR-221 & miR-222 (194)	miR-218 ↓ (54), miR-221 ↑ (211), miR-222 ↑ (212)
			P65/RelA	miR-155 (96), miR-3151 (175)	
GR 5'-TGTTCT-3' (213)	Induced	Activated (214)		miR-124 (215), miR-142–3p (216), miR-150–5p (217)	miR-142–3p ↓ (218)

[1]Bold font indicates *Italics indicate not direct target I ↑: upregulated, ↓: downregulated

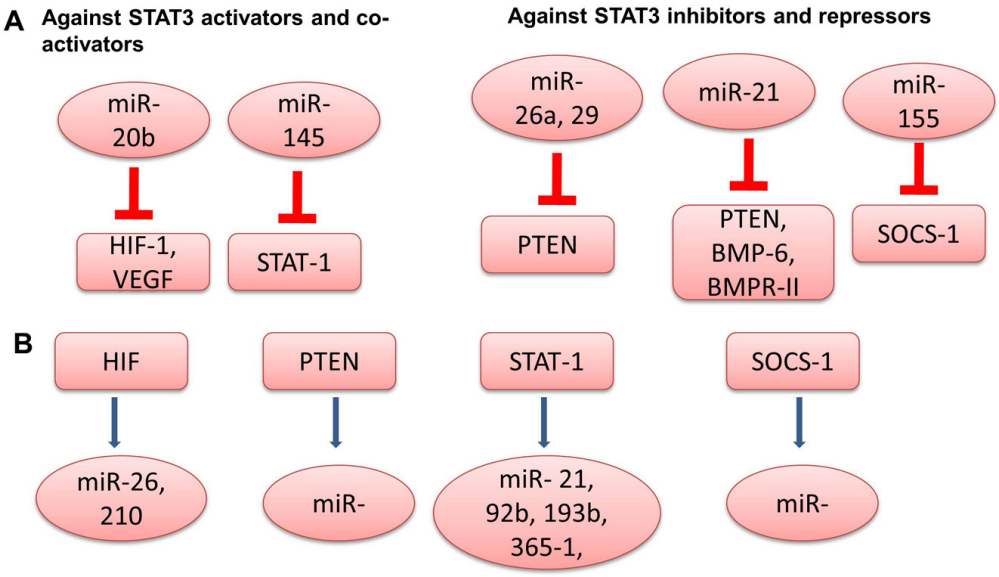

Figure 4. miRNAs negatively regulating STAT3 activators and co-activators and STAT3 inhibitors and repressors (A) and their reciprocal regulation by STAT3 signaling components (B).

site has been shown in the promoters of different miRs including miR-21 (90, 107) and miR-148a, miR-132, miR-181b-1, miR-148b, miR-193a, miR-340, miR-335, miR-210 and miR-187 (36). 130-bp regions containing two predicted STAT3 binding sites upstream of the miR-21 genes have been reported in various vertebrate species. A stable distance between miR-21 and the STAT3 sites throughout all vertebrates strongly suggests their functional correlation (107). Schematic representation showing miRNAs which negatively regulates STAT3 activators and co-activators, and STAT3 inhibitors and repressors are depicted in Figure 4A. Our group has recently shown that STAT3 is negatively regulated by Let-7a and it regulates miR-21 in HPV-positive cervix cancer tissues (60) and cell lines (59). STAT3 transactivates another miR, miR-181b-1. STAT3 and miR-181b-1 expression levels are positively correlated in colon adenocarcinomas as well as in MCF-10A cells during transformation (36). miR-20b reduces VEGF expression through HIF-1 and STAT3 mediation in breast cancer cells (108). Recent data have identified STAT3 as a novel target of let-7a in hepatocellular carcinoma (109). miR-21 negatively regulates PTEN, a negative regulator of STAT-3 and MMP-2, thus up-regulating MMP-2 expression in cardiac fibroblasts (110). SOCS-1 has been implicated in the negative regulation of IL-6R/Jak/STAT pathways (111). miR-19a and miR-19b has been shown to target SOCS-1 (negative regulator of STAT3) and suggest a role of miR-19 in the IL-6 anti-apoptotic signal in the pathogenesis and malignant growth of multiple myeloma (112). Some of the important components of STAT3 signaling as direct targets and regulators of miRs are shown in Figure 4B.

7.4. "Yin and Yang1" (YY1)

The ubiquitous cellular factor YY-1 also known as UCRBP, δ, NF-E1, CF1, NMP-1, has been reported to play a critical role in tumorigenesis (113) and HPV infection (114). YY-1 can function as both a positive (115–117) and a negative (118, 119) regulator of cellular and viral gene expression. The extrachromosomal or integrated HPV16 DNA isolated from malignant cervical biopsies contains mutated or deleted YY1 sites upstream of the p97 start site (120, 121) which result in increased p97 transcription, origin of replication (ori) function, initial plasmid amplification and virus immortalization capacity. It has been noted that YY1 binding to a critical motif adjacent to the p97 transcription start site downregulates the HPV16 E6/E7 promoter (122). YY1 regulates miR-190 expression in the primary hippocampal cultures (123). miR-29 is epigenetically silenced by an activated NF-κB-YY1 pathway in rhabdomyosarcoma cells and primary tumors (124).

8. STRATEGIES TARGETING MIRS IN CARCINOGENESIS PROCESS

Accumulating data suggest that miRNAs might be used as potential therapeutic tools for several diseases including cancer. For example, the activity of miRNAs was inhibited using miRNA inhibitors for miR-21 and the cell growth in HeLa was found to increase after miRNA inhibition (125). The reporter vectors containing miR binding sites for target miRs are constructed. These binding sites are made by hybridizing oligonucleotides containing the miRNA binding site and cloned them into the 3' UTR

Table 4. Various strategies for targeting/overexpression of microRNAs

Strategy	Advantages	Reference
Locked nucleic acid (LNA)	Unprecedented binding affinity to complementary RNA molecules which is governed by conformational restriction	(132)
mRNA Decoy	It will be more difficult for diseased cells to evolve resistance to RNA decoy	(219)
Modified anti-miRNA oligonucleotides (AMOs) or Antagomirs	Effectively silence miRNAs *in vivo*. Enable the study of gene regulation *in vivo* by tissue specific miRNAs	(130)
miR Mimics	Specifically bind to essential sites within target RNAs	(220)
miRNA Inhibitory Transgenes or miRNA sponges	Convenience of making dominant negative transgenics over knockouts and applicability to a broader range of model organism and cell lines	(134)
miR Hairpin	Allow use of DNA vector-based short hairpin (sh)RNA for RNA interference	(221)

of luciferase vector. miRNA inhibitors inhibit the ability of the endogenous miR by inhibiting the expression of the reporter gene containing the miRNA binding site (126–128). Another approach uses 2-O-methyl oligoribonucleotides (2-O-Me-RNA). These molecules stoichiometrically bind and irreversibly inactivate miRNAs. Antisense 2-O-Me-RNA have been used to specifically down-regulate miRNAs in human cells (126). Knockdown of miR-21 using 2-O-Me-RNA triggered activation of caspases and increased cell death in glioblastoma cells (129). Antagomirs are chemically modified cholesterol conjugated single strand RNA molecules complementary to a mature miRNA. miR-122 antagomir administration showed upregulation of genes with 3'UTR miR-122 recognition motifs, leading to a reduction in plasma cholesterol levels (130). For miRNAs that act as tumor suppressors, it may be of interest to develop *in vivo* expression systems. For example, let-7, a tumor suppressor family, may provide useful strategy to control tumor growth by ectopically overexpressing its family (131). Locked nucleic acids (LNAs) comprise a class of bicyclic high-affinity RNA analogues in which the furanose ring in the sugar-phosphate backbone is chemically locked in an RNA-mimicking N-type (C3-endo) conformation by the introduction of a 2-*O*,4-C methylene bridge (132) (see Table 4). LNA-ISH (*in-situ* hybridization)-based detection of miR-21 overexpression indicates important diagnostic marker of colorectal carcinogenesis (133). The sponge mRNA, which contains multiple target sites complementary to a miRNA of interest, is a dominant negative method (134). Down-regulation of miRNA-574–5p using miR-574–5p sponge *in vivo* significantly abrogated the enhanced tumor progression induced by TLR9 signaling in human lung cancer (135). Expression of constitutively active TORC1 has been shown to attenuate the miR-21 sponge-mediated suppression of proliferation and migration of renal cancer cells (136). miRNA target decoys are endogenous RNA that can negatively regulate miRNA activity. An mRNA decoy has been designed and applied in the research of miR-133 in the pathogenesis of cardiac hypertrophy. The suppression of miR-133 decoy sequences induced cardiac hypertrophy (137). The various strategies to target miRNAs are summarized in Table 4.

9. PERSPECTIVE - PROGNOSTIC SIGNIFICANCE OF MIRS IN CERVICAL CANCER

Despite available data that progressive cervical or other cancer lesions will have unique set of miR, not much work has been carried out to harvest the prognostic significance of miRs in HPV infection or cervical cancer in clinical settings. Altered miR expression has been associated with cancer progression and miR profile as prognostic factor can provide valuable tool in treatment of cervical cancer patient. Huang *et al.* showed that low expression of hsa-miR-100 and hsa-miR-125b showed poor prognosis in small cell carcinoma of the cervix patients (63). Some studies have shown potential of miRs as prognostic marker in HPV-mediated cancers. Thirty-nine cancer-associated miRs were found near 37 HPV integration sites. miR-21, miR-142, miR-301a and miR-454 were present at HPV16 integration site at chromosome number 17q23.1 (138). Among these miRs, overexpressed miR-21 was detected in a variety of cancers. Hu *et al.* used the recursive feature elimination (RFE) technique to rank the relative importance of each miRNA in cervical cancer samples. Among top 10 miRs, miR-200a and miR-9 were described as promising miRs that could predict patient survival (68). Recently, some studies have indicated that aberrant and circulating miRNA expressions may have potential prognostic value in different other malignancies (139). Similarly in human lung cancer cells, an association has been shown between high expression of miR-31 and poor survival of stage I–III squamous cell carcinoma patients without any treatment prior to surgery (140). The tumor suppressor DICER1 was identified as a target of miR-31 and the expression of miR-31 can repress DICER1 activity.

Recently, miRNA mimic-based therapy has been tested in preclinical models of cancer. Several studies have investigated the miRNA mimics

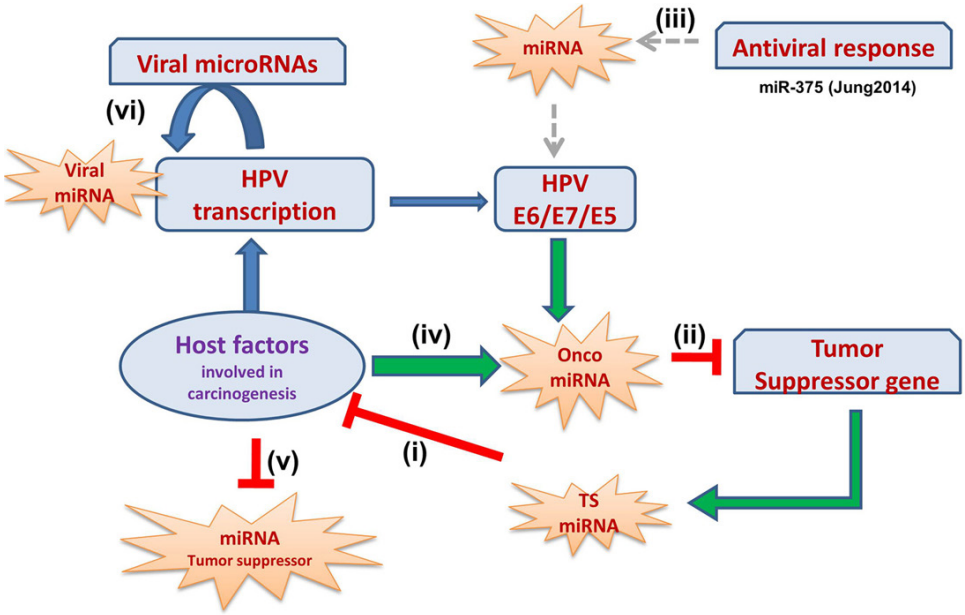

Figure 5. Schematic representation of potential miRNA-mediated regulatory mechanism that may operate during HPV-induced cervical carcinogenesis. Briefly, (i) miRNA that regulate expression of host factors involved in HPV-mediated carcinogenic signaling particularly in altering the expression and activity of transcription factors essentially required for expression of viral oncogenes. (ii) or inhibition of tumor suppressor genes. (iii) In contrast, miRNAs could specifically be involved in generic and HPV-specific antiviral response may have regulatory role independent of HPV infection. Apart from the above, cells undergoing oncogenic transformation may directly influence expression of (iv) oncomiR and (v) tumor suppressor miR. Green arrow-activation/upregulation, red arrow-inhibition/downregulation, grey arrow-unknown.

in preclinical animal models of lung cancer and mesothelioma (141). A phase 1 trial of TargomiRs, MesomiR-1, focused on miRNA mimic-based therapy for thoracic cancer was initiated in 2014 (141). Similarly, there are on-going clinical trials and preclinical studies targeting miRNAs against different cancers (142). Rosetta Genomics is now offering a panel (miRview-mets2) to clinicians so that the origin of metastatic cancers can be identified where the primary origin of metastasis is uncertain (143). Although the current status of miRNA-based clinical applications is narrow, further advancement in miRNA studies will hopefully translate miRNA-based cancer therapeutics into a clinical reality.

These findings suggest that miR signatures apart from understanding the basic biology could also provide useful information as novel prognostic indicators or markers of treatment response, which may contribute to improved selection of patients to classify tumors according to clinicopathologic variables currently used to predict disease progression. However, these initial findings need additional experiments based information to investigate how altered miRNA expression would manifest the biological consequences in the development of cervical cancer. Taken together, we propose a schematic representation of potential miRNA-mediated regulatory mechanism that may operate during HPV-induced cervical carcinogenesis (Figure 5).

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Abbreviations: HPV: Human papillomavirus, miR/miRNA: MicroRNA, STAT3: Signal transducer and activator of transcription, URR: Upstream regulatory region

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