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Interplay Between HPV Oncoproteins and MicroRNAs in Cervical Cancer

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1. Introduction

For close to a century, researchers have known that Papillomavirus infections in humans cause a variety of benign proliferations including warts, epithelial cysts, intraepithelial neoplasias, oral laryngeal, pharyngeal papillomas and other types of hyperkeratosis. However the molecular mechanisms involved are far from understood. HPV has been detected in more than 90% of cervical cancers and therefore implicated as the main etiological agents in cervical cancer. The pathogenesis of cervical cancer is well-known to involve a multi-step process that includes the transformation of normal cervical epithelium to pre-neoplastic cervical intraepithelial neoplasia that is subsequently transformed to invasive cervical cancer. Although the causal relationship between high-risk human papillomavirus (HPV) infection and cervical cancer has been well-documented in epidemiologic and functional studies, HPV infection alone is not sufficient to induce the malignant transformation of HPV-infected cells. Hence, other unidentified genetic alterations, such as microRNAs the *master switches*, are required. A class of molecules discovered quite recently, microRNAs (miRNAs), appear to play a significant role in cell proliferation and differentiation, and aberrant miRNAs are associated with several cancers. An new era focusing on micro RNAs, and the studies on HPV and host miRNA interactions will continue shedding more light on understanding of the HPV life cycle and the mechanistic underpinnings of HPV-induced oncogenesis.

These small non-coding RNAs can contribute to the repertoire of host pathogen interactions during viral infection. This interplay has important consequences, both for the virus and the host. There has been reported evidence of host-cellular miRNAs modulating expression of various viral genes, thereby playing a pivotal role in the host-pathogen interaction network. In the hide-and-seek game between the pathogens and the infected host, viruses have evolved highly sophisticated gene-silencing mechanisms to evade host-immune response. Recent reports indicate that virus also encode miRNAs that protect them against cellular antiviral response. Furthermore, they may exploit the cellular miRNA pathway to their own advantage. This chapter aims to summarize our current knowledge about miRNA profiles in cervical cancer cell lines and tissues as well as recapitulate recent updates on miRNA-induced gene-silencing mechanism; modulating host-virus interactions of HPV integrated Cervical Carcinomas.

2. Human papillomaviruses and cervical cancer

Cervical cancer is the second most common life-threatening cancer among women worldwide, with 493,243 new cases and nearly 273,505 deaths per year (Parkin et al., 2005, 2006). In 2010, there were an estimated 12,200 new cases and an associated 4,210 deaths, accounting for approximately 1% of cancer deaths in women (Jemal et al., 2010). In 1995 the World Health Organization (WHO) declared HPV as a known carcinogen for causing factor for cervical cancer, because DNA of mucosal high-risk HPV types could be detected in almost all cervical cancers (Walboomers et al., 1999). Persistent infection with oncogenic high-risk subtypes of human papillomavirus (HPV) leads to cervical cancer (zur Hausen 2002) and over 50% of the cases are HPV-16 (Walboomers et al., 1999). In cancer development, HPV-16 early proteins E6 and E7 are often believed to act as oncoproteins as both are crucial for immortalization and transformation of cervical keratinocytes (Munger et al., 2004). The E6 and E7 oncogenes work synergistically to deregulate cell cycle controls through a variety of mechanisms. The E6 oncogene promotes ubiquitination and proteasomal degradation of the tumor suppressor protein p53 and also deregulates the cell cycle (Thomas et al., 1999). The E7 protein binds to and inactivates the function of retinoblastoma protein Rb and the related tumor suppressor proteins p107 and p130. It disrupts the complex between Rb and the E2F transcription factor family, which controls the expression of genes involved in cell-cycle progression. Thus, destabilization of p53 and hypophosphorylated pRb by the expression of two viral oncoproteins E6 and E7 promotes chromosomal instability, foreign DNA integration, and other mutagenic events in the cell.

2.1 HPV Oncoproteins

HPVs encode two major oncoproteins, E6 and E7, which are consistently expressed in cervical carcinomas. E6 and E7 lack intrinsic enzymatic activities and transform cells by stimulating cell growth and inactivating tumor suppressor pathways. Expression of HPV16 E6/E7 oncoproteins in primary human epithelial cells causes genomic instability.

2.1.1 E6 protein

The E6 protein of HPV is a 18 kDa phosphoprotein, which is localized in the nucleus and in non-nuclear membranes. E6 is a critical factor in tumor formation and acts to destabilize the tumor suppressor p53. The p53 tumor suppressor protein, in turn, regulates the transcription of several genes that keep cell proliferation in check by inducing cell cycle arrest, DNA repair, or apoptosis. The E6 protein forms a complex with p53 and the cellular ubiquitin ligase causing a deregulation of the cell cycle control at the G1/S and G2/M check points, an important step for the replication of HPV, because a productive infection cycle is only possible in cells, which are in the S-phase of the cell cycle. However, this cell cycle manipulation can lead to activation of oncogenes or inactivation of tumor suppressors and consequent DNA damage cannot be repaired. This leads to genetic instability and to malignant transformation of high-risk HPV-infected cells (Fehrman and Laimins 2003). Another important way how E6 proteins of genital HPV contribute to transformation is the activation of the human telomerase reverse transcriptase promoter, which controls the transcription of the catalytic telomerase subunit. E6 proteins of cutaneous HPV do not

interact with p53 or E6-AP and do not degrade p53 (Elbel *et al.* 1997). Furthermore E6 proteins of both cutaneous and anogenital HPV are able to target the proapoptotic protein for ubiquitin-dependent degradation by assembling E6-AP, thereby inhibiting apoptosis.

2.1.2 E7 protein

E7 is a 11 kDa protein with a zinc finger motif. It acts as an oncogene in genital high risk HPV and is able to immortalize primary foreskin keratinocytes. The major part of the transforming potential of E7 is due to binding and induction of ubiquitin-dependent degradation of the tumor suppressor retinoblastoma protein (Rb) (Berezutskaya and Bagchi 1997). The competitive binding of E7 to Rb and its degradation lead to segregation of the transcription factor E2F. In the G1-phase, E2F is inactivated in a complex with Rb. After segregation, E2F can induce the expression of genes, which are important for DNA synthesis and cell cycle control. Additionally E7 can bind the inhibitors of cyclin dependent kinases p21CIP1 and p27KIP1 and inhibit their functions (Münger *et al.* 2001). Both events direct the cell into the S-phase and enable the viral replication.

3. MicroRNA biology

One of the most significant recent advances in biomedical research has been the discovery of ~22-nt-long class of noncoding RNAs designated as microRNAs (miRNAs). MicroRNAs are small, non-coding RNAs that regulate gene expression (Ambros *et al.*, 2003) it function by binding to the 3' UTRs of their target messenger RNA (mRNA), whereby they induce mRNA degradation or repression of translation. The functions of miRNAs are still largely unknown but they appear to be integral to modulation of gene expression and cell behavior. These regulatory RNAs provide a unique level of posttranscriptional gene regulation that modulates a range of fundamental cellular processes.

MiRNAs were first discovered in *C. elegans* (Lee *et al.*, 1993). They have since been found to be conserved across many species, and may regulate thousands of targets via the RNAi pathway (Lewis *et al.*, 2005). Most miRNAs are transcribed by RNA polymerase II, have a Cap, and are polyadenylated (Cai *et al.*, 2004). They are often processed from polycistronic transcripts (Lee *et al.*, 2002). Following transcription, the large primary miRNA transcripts are processed into precursor-miRNAs by the protein Drosha. Pre-miRNAs are hairpin-like structures with characteristic 2 nt 3' overhangs (Figure.1). They are exported to the cytoplasm by exportin 5 (Lund *et al.*, 2004), where further processing into miRNA duplexes by the protein Dicer. MicroRNA duplexes associate with the RISC complex but only one strand, the mature miRNA; remains associated with it and are delivered to its target (Schwarz *et al.*, 2003; Khvorova *et al.*, 2003). The fate of target mRNAs depends on the degree of complementarity with the miRNA. Commonly, the 5' 2-8 nt of the miRNA (called the seed sequence) is complementary to the target, and the remaining miRNA contains many mismatches. A low degree of complementarity results in translational repression, whereas a high degree of complementarity results in cleavage of the mRNA followed by its eventual destruction (Kim, 2005).

To date, more than 10,000 miRNAs have been annotated in 96 species, including over 700 human miRNAs (miRBase v14.0). More than 50% of miRNA genes are located in cancer associated genomic regions or in fragile sites, suggesting that miRNAs should be important

in cancer formation (Calin et al., 2004). Some recent studies show that miRNAs control many crucial biological activities, including cellular proliferation, differentiation and apoptosis (Esquela-Kerscher and Slack, 2006; Zhang et al., 2007). The main function of miRNA is to repress the expression of target mRNA by cleavage or translational silencing, which depends on their complementation with the 3'-untranslated region (3'UTR) of target mRNAs (Calin and Croce, 2006; Esquela-Kerscher and Slack, 2006; Garzon et al., 2005). By using highthroughput miRNA microarray analysis, compared with the adjacent normal tissues, deregulation of the expression of miRNAs has been reported in different kinds of human cancer (Zhang et al., 2007; Lee et al., 2008), including cervical cancer (Lui et al., 2007; Lee et al., 2008). The aberrant expression of miRNA in cancer indicates the possible function of miRNAs in cancer development (Calin and Croce, 2006). Current evidence indicates that viruses use these miRNAs to manipulate both cellular and viral gene expression. Furthermore, viral infection can exert a profound impact on the cellular miRNA expression profile.

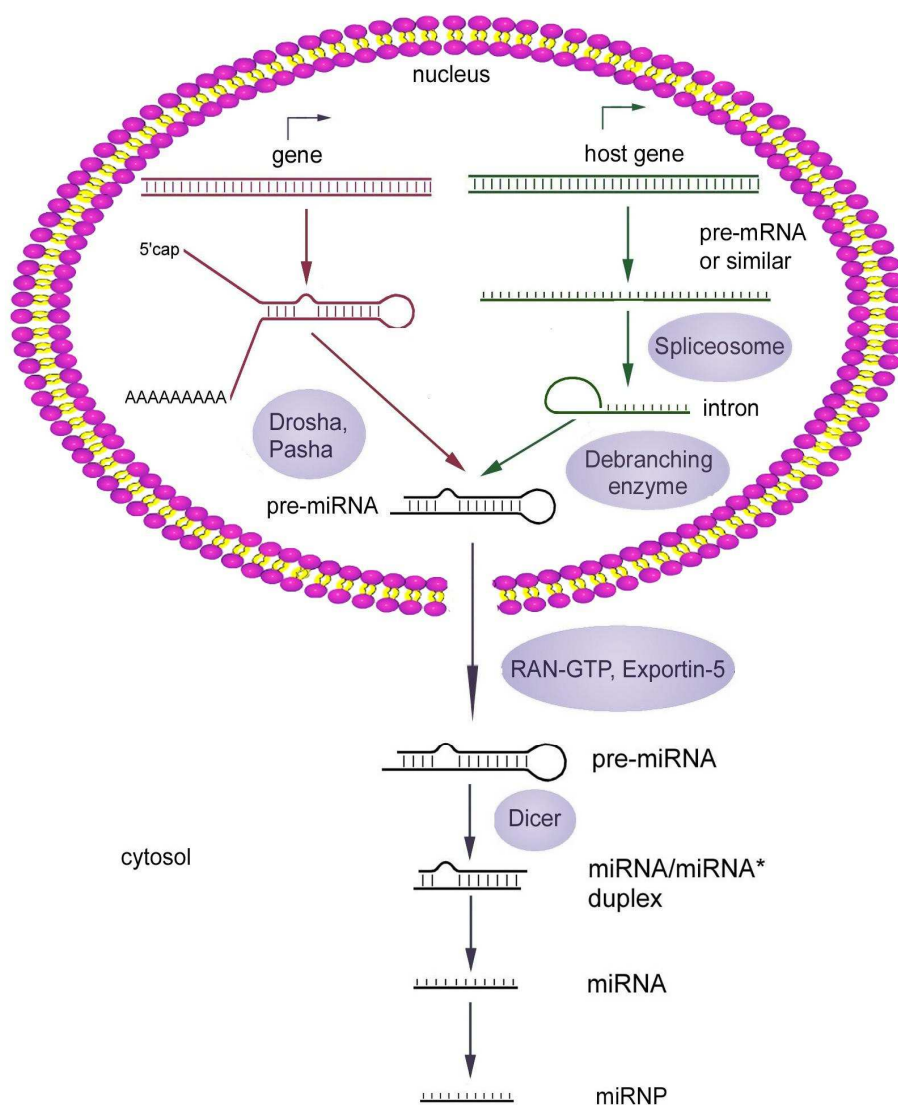


Fig. 1. Biogenesis of MicroRNA

3.1 MicroRNA and cancer

Many studies showed that miRNAs are aberrantly expressed in cancer, suggesting their role as a novel class of oncogenes or tumor suppressor genes. Many studies have been performed to investigate the contribution of miRNAs to carcinogenesis. The findings that miRNAs have a role in cancer are supported by the fact that about 50% of miRNA genes are localized in cancer-associated genomic regions or in fragile sites or integration sites of high-risk HPVs (Calin et al., 2004). Integration may alter miRNA expression via deletion, amplification, or genomic rearrangement. In a recent study, Lu et al., (2005) profiled miRNA expression patterns of human cancers and found differential expression for each cancer type. Depending on the nature of their targets, miRNAs can function as either tumor suppressor genes or oncogenes. For example, overexpression of miRNAs that target oncogenes can lead to increased destruction of these oncogenes and therefore tumor suppression. Conversely, overexpression of miRNAs that target tumor suppressors can result in increased oncogenic activity and tumor formation. Regulation mediated by these genes has possibly a large impact on gene expression because, according to computational predictions, a single miRNA can target dozens of genes. MicroRNAs have been shown to regulate the oncogenes Bcl 2 and Ras, as well as the tumor suppressor pRb. MiR-15 and miR-16 were the first miRNAs shown to be associated with cancer; they are underexpressed in chronic lymphocytic leukemia (CLL) (Calin et al., 2002). They regulate the *Bcl-2* oncogene, which is overexpressed in many cancers (Cimmino et al., 2005). The *let-7* family of miRNAs regulates the Ras oncogenes, which contain activating mutations in about 15-30% of cancers (Johnson SM, et al., 2005) and down regulation of the *let-7* family of miRNAs results in the up regulation of *Ras*, which is most pronounced in lung cancers (Takamizawa J, et al., 2004).

3.2 Altered microRNA signatures in cervical cancer

Many authors have reported that each cancer tissue has a specific microRNA signature and microRNA based cancer classification is a very effective and potential tool (Lu et al., 2005). It is interesting to speculate that miRNA expression signatures have been shown to be promising biomarkers for Cervical Cancer prognosis (Xiaoxia Hu et al., 2010). Thus miRNA expression patterns may serve as potential biomarkers of pre-invasive cervical disease and potential therapeutic targets. Keeping in view the immense impact of microRNAs expressional profile in cancer biology, conducted surveys on expressional patterns of miRNAs in cervical cancer suggested that beyond HPV, microRNAs play a major role in cervical cancer pathogenesis and progression (Reshmi and Pillai 2008). Micro-RNA expression profile in cervical cancer cell lines found that of 174 miRNAs which could be grouped into 46 different miRNA species, miR-21, miR-24, miR-27a, and miR-205 were most abundant in cervical cancer or cervical intraepithelial neoplasia derived cell lines (Wang et al., 2008). MicroRNA array analyses for age-matched normal cervix and cervical cancer tissues, in combination with Northern blot verification identified deregulated miRNAs in cervical cancer tissues. Down regulation of with miR-126, miR-143, and miR-145, miR-218, and miR-424 and up regulation of miR-15b, miR-16, miR-146a, and miR-155 had shown in Table 1 and 2 respectively. Functional studies showed that both miR-143 and miR-145 are suppressive to cell growth. When introduced into cell lines, miR-146a was found to promote cell proliferation. Another study suggested that overexpression of miR-17-5p, miR-20a, miR-21, miR-92, miR-106a, and miR-155 could be considered a miRNA signature of solid tumors

(Volinia *et al.*, 2006). Eighteen miRNAs were upregulated in solid tumors where 15 were downregulated in cervical cancer tissues. The increased expression of miR-15b, miR-16, miR-146a, miR-155, and miR-223 observed in cervical cancer tissues has also been implicated in the development of other human cancers. Another study suggests that altered miRNA expression patterns seen in early stage invasive squamous cell carcinomas (ISCCs) and normal epithelial tissues of the cervix and findings suggest that miR-127 may be a marker for lymph node metastasis of ISCCs and that miR-199a may be a potential therapeutic target for future cervical cancer therapy (Lee *et al.*, 2008).

miRNA	Chromosome	Putative Function
hsa-miR-210	11	oncogenic
hsa-miR-182	07	og/ tsg
hsa-miR-183	08	og/ tsg
hsa-miR-200c	12	tumour suppressor
hsa-miR-203	14	og/ tsg
hsa-miR-193b	16	oncogenic
hsa-miR-34a	01	og/ tsg
hsa-miR-31	11	og/ tsg
hsa-miR-210	11	og/ tsg
hsa-miR-27a	19	og/ tsg
hsa-miR-503	X	og/ tsg
hsa-miR-27b	09	og/ tsg
hsa-miR-199a	19	og/ tsg
hsa-miR-199b	09	og/ tsg
hsa-miR-146a	05	og/ tsg
hsa-miR-133a	18	og/ tsg
hsa-miR-133b	06	og/ tsg
hsa-miR-214	01	og/ tsg
hsa-miR-127	14	og/ tsg

og-oncogene; tsg-tumor suppressor gene

Table 1. MicroRNAs overexpressed in cervical cancer cell lines.

miRNA	Chromosome	Putative function
hsa-miR-126	09	og/ tsg
hsa-miR-145	05	og/ tsg
hsa-miR-451	17	og/ tsg
hsa-miR-195	19	og/ tsg
hsa-miR-143	05	og/ tsg
hsa-miR-199b	09	og/ tsg
hsa-miR-1	01	og/ tsg
hsa-miR-495	14	og/ tsg
hsa-miR-497	17	og/ tsg
hsa-miR-133b	06	og/ tsg
hsa-miR-223	X	og/ tsg
hsa-miR-126-AS	09	og/ tsg
hsa-miR-150	19	og/ tsg
hsa-miR-376a	14	og/ tsg
hsa-miR-214	01	og/ tsg
hsa-miR-487b	14	og/ tsg
hsa-miR-10b	02	og/ tsg
hsa-miR-218	04	og/ tsg
hsa-miR-149	02	og/ tsg
hsa-miR-203	14	og/ tsg

og-oncogene; tsg-tumor suppressor gene

Table 2. MicroRNAs underexpressed in cervical cancer cell lines.

3.3 Modulation of cellular microRNA regulation by HPV oncoproteins

Deletions or mutations in miRNA genes, as well as aberrant expression of oncogenic or tumor-suppressive miRNAs, are common in human cancers (Calin and Croce 2006; Wang et al. 2008), but the causes for their aberrant expression are poorly understood. Although many human viruses produce their own viral miRNAs in the course of virus infection (Tang S et al., 2008 & Umbach et al. 2008), but recently various studies reported on viral proteins regulation of cellular miRNA expression. Deregulation of oncogenic and tumor suppressive miRNAs in human cervical cancer is associated High-risk human papillomavirus (HPV) integration. Cervical cancer represents a unique tumor model for understanding how viral E6 and E7 oncoproteins deregulate the expression of the microRNA clusters via downstream targets of the transcription factors (Figure.2). It is well recognized that cellular miRNAs play

important roles in the regulation of cellular genes. Recent data designate that cellular miRNAs can also target the genetic material of invading viruses. Moreover, Latest host viral interaction studies of HPV integrated cervical cancer samples supports the evidence of interplay between the viral oncoproteins and microRNA expressions in oncogenic HPV-infected cells.

3.3.1 hsa-miR-34a

Recently, miR-34a was identified as a direct transcriptional target of cellular transcription factor p53 (He et al. 2007; Raver-Shapira et al. 2007). This transactivation of miR-34a expression is triggered by the binding of p53 to a consensus p53 binding site identified in the miR-34a promoter region. Since HPV E6 oncoprotein destabilizes p53 during virus infection, one may assume a down-regulation of miR-34a expression in most cervical cancer tissues with oncogenic HPV infection. Interestingly, Wang et al discovery shows that at all stages of pathogenesis induced by the high-risk HPV types, the E6 destabilization of the tumor suppressor p53 down-regulates the tumor-suppressive miR-34a, leading to the elevated expression of cell cycle regulators and cell proliferation (Wang et al., 2009). These intimate interplays among viral E6, p53, miR-34a, and E7 place miR-34a in a central role in a well-known viral oncoprotein-tumor suppressor network.

3.3.2 hsa-miR-23b

Au Yeung et al., suggesting miR-23b is often downregulated in HPV-associated cervical cancer. Interestingly, urokinase-type plasminogen activator (uPA), the miR-23b target, is detected in cervical cancer, but not in normal cervical tissues. Thus, the importance of miR-23b and uPA in HPV-associated cervical cancer development is investigated. HPV-16 E6 oncoprotein was found to decrease the expression of miR-23b, increase the expression of uPA, and thus induce the migration of human cervical carcinoma SiHa and CaSki cells. uPA is the target gene for miR-23b as the miR repressed uPA expression and interacted with the 3'-untranslated region of uPA mRNA. From the above, miR-23b/uPA are confirmed to be involved in HPV-16 E6-associated cervical cancer development (Au Yeung et al., 2011).

3.3.3 hsa-miR-218

MicroRNA-218 (miR- 218) is specifically underexpressed in cell lines, cervical lesions and cancer tissues containing integrated HPV-16 DNA compared to the normal cervix. Martinez et al., studies revealed that exogenous expression of the HPV-16 E6 oncogene reduced miR-218 expression, and conversely, RNA interference of E6/E7 oncogenes in an HPV-16 positive cell line increased miR-218 expression. Exogenous expression of miR-218 in HPV-16 positive cell lines decreased expression of the epithelial-specific gene LAMB3, which is involved in cell migration and tumorigenicity (Martinez et al., 2008)

3.3.4 hsa-mir-29

Yang et al established a putative HPV-associated miRNA-mRNA regulatory network, showing that miR-29 is the most highly enriched. Studies found that YY1 and CDK6 were both positively correlated with E6/E7 RNA expression and targeted by tumour-suppressive

miR-29 (Yang et al., 2011). Evidence of miR-29 involvement in HPV infection was further verified in patient samples and by various experimental approaches suggests that HPVs have oncogenic properties at least in part by reshaping the milieu of cellular miRNAs. miR-29 restrains cell cycle progression and induces apoptosis via YY1 and CDK6 promoting malignant transformation induced by HPV, although the abnormality of miR-29 in HPV-infected cells might be regulated in an indirect way.

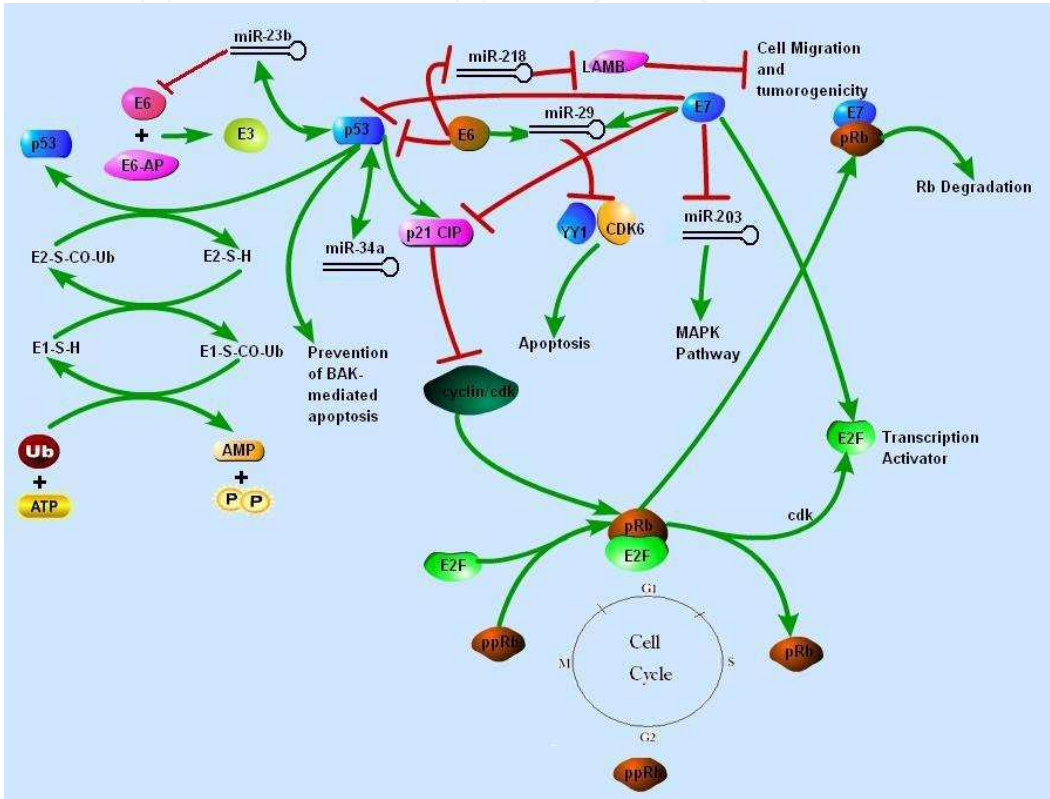


Fig. 2. Interaction of HPV oncoproteins and regulation of MicroRNAs in Cervical Carcinoma

3.3.5 hsa-miR-203

Recent studies indicated that the HPV E7 protein interferes with the normal upregulation of miR-203 expression upon differentiation, which may occur through the mitogen-activated protein (MAP) kinase/protein kinase C (PKC) pathway. Interestingly, the MAPK pathways induce all these transcription factors (Melar et al., 2010). Several downstream targets of p63, CARM-1, p21, and Bax, were also increased in E7-expressing cells, and their levels were inversely correlated with amounts of miR-203. Since the MAPK/protein kinase C (PKC) pathway is also implicated in regulating keratinocyte differentiation, studies suggests that miR-203 levels were affected by the MAPK/PKC pathway signaling and if HPV E7 interfered with the activation of this pathway.

Recent studies indicate that human cellular miRNAs can also target the genetic material of invading HPV viruses. It also gives the virus an opportunity to modulate the host to suite its needs. Thus the range of interactions possible through miRNA-mRNA cross-talk at the host-pathogen interface is large. These interactions can be further fine-tuned in the host by changes in gene expression, mutations and polymorphisms. In the pathogen, the high rate of

mutations adds to the complexity of the interaction network. Though evidence regarding microRNA mediated cross-talk in viral infections is just emerging, it offers an immense chance not only to understand the intricacies of host-pathogen interactions but also to develop novel biomarkers and therapeutics.

4. Conclusion

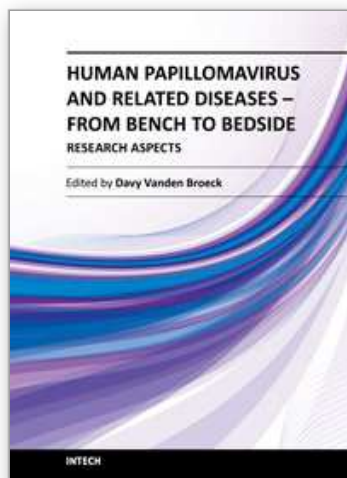
On the basis of these observations, we suggest a new dimension to HPV-initiated carcinogenesis. HPV modulates the expression of numerous cellular microRNAs that are likely contribute to viral pathogenesis. Surprisingly, recent studies have led to the identification of cellular microRNA regulation by HPV oncoproteins and viral regulation of expression of a tumor suppressor miRNAs. The known data provides evidence that this intimate interplay of oncoproteins and microRNAs could disclose new ways for cancer diagnosis, prognosis evaluator and therapy.

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Cervical cancer is the second most prevalent cancer among women worldwide, and infection with Human Papilloma Virus (HPV) has been identified as the causal agent for this condition. The natural history of cervical cancer is characterized by slow disease progression, rendering the condition, in essence, preventable and even treatable when diagnosed in early stages. Pap smear and the recently introduced prophylactic vaccines are the most prominent prevention options, but despite the availability of these primary and secondary screening tools, the global burden of disease is unfortunately still very high. This book will focus on epidemiological and fundamental research aspects in the area of HPV, and it will update those working in this fast-progressing field with the latest information.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Reshmi G and M.Radhakrishna Pillai (2012). Interplay Between HPV Oncoproteins and MicroRNAs in Cervical Cancer, Human Papillomavirus and Related Diseases - From Bench to Bedside - Research aspects, Dr. Davy Vanden Broeck (Ed.), ISBN: 978-953-307-855-7, InTech, Available from:

<http://www.intechopen.com/books/human-papillomavirus-and-related-diseases-from-bench-to-bedside-research-aspects/interplay-between-hpv-oncoproteins-and-micrnas-in-cervical-cancer>

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