e-ISSN 2371-770X

Modern Medical Laboratory Journal

DOI:10.30699/mmlj17.3.1.88

The Regulatory Role of Differential Expressed MicroRNAs and Viral Oncoproteins in Angiogenesis of Human Papillomavirus-Related Cancer

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KEYWORDS

Cervical cancer;
HPV;
E6 and E7;
P53;
Angiogenesis

Article Info

Received 2020/09/05;
Accepted 2020/10/03;
Published Online 2020

ABSTRACT

According to the performed study, the most important known cause of cervical cancer is contamination with HPV infection which is the main cause known for complex molecular changes leading to the neck epithelial cells, and if the virus is of the high risk type, it leads to cervical cancer. Studies and analysis of performed experiments, have led to the belief that some miRNAs play a key role in cancer prognosis and the evaluation of them can indicate the existence of cervical cancer. Analysis results indicate that in cervical cancer, some oncoproteins such as E5, E6, and E7, begin their activity when the HIV infection starts. Each of these oncoproteins have various functions. They can cause disorders or performance improvements. The present paper provides a brief review of these oncoproteins as well as miRNAs involved in cervical cancer.

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Introduction

Cancer is a multi-factor disorder arisen by molecular evolution [1, 2]. Cervical cancer is among the most prevalent malignant tumors in women, causing 10% to 15% of female cancer mortalities. This is the second most prevalent type of cancer leading to death among women [3]. The highest death rate from cervical cancer is recorded in eastern Africa and the lowest rate is observed in west Asia [4]. Persistent infection with Carcinogenic human papillomavirus [5], is the main cause of 95% of

invasive cervical cancer cases, including skin squamous cell carcinoma (SCC) cancer and Adenocarcinoma (AC) cancer [6]. A biomarker or other factor is needed to assess the initial prognosis of metastasis [7]. One of the methods in effective prevention of the progression of cervical cancer is detecting viral nucleic acids in oncologic screening programs [8]. Gradual accumulation of genetic and epigenetic changes in the HPV-infected cells is also crucial in the final progression of cervical cancer. Through the mutative properties of cervical cancer, the presence of unconventional nucleotide variations in Tp53, PTEN, PIK3CA, STK11, KRAS genes can be depicted [9, 10]. According to the results obtained from Pap Smear screening program, which has caused a considerable reduction of cervical cancer cases, this is the third most common globally known cancer type [7]. And based on evidence obtained through studies and observations, the survival ond treatment rate of this type of cancer is 80% to 90% during the initial stages (stage I and II) and 60% during stage III, but the prognosis of that in during the recurrence stage of the disease, can be considered negligible [11]. Single nucleotide polymorphism (SNP) among tumor suppressing genes and oncogenes plays a key role in genetic sensitivity to cervical cancer [7]. Recent studies indicate that the use of hormonal therapy replacement, High risk exposure to HPV, genetic factors, and smoking habits play important role in cervical cancer pathogenesis [12]. Dangerous HPVs include oncoproteins which deactivate certain tumor suppressing proteins, such as E6 and E7 oncoproteins [13]. One of the important signaling pathways contributing to cell survival and reproduction is mediated by Oncogenic Ras. The mutated version of Ras will help by guiding the cells towards tumor progression via such effective downstream pathways as PI3K (Phosphorus Inositol 3-kinase), PKB (Protein kinase B)/AKT, and MAP kinase (MAPK), while E6 will activate the MAPK pathway. The E7 expressing cells in a starvation condition, act opposite of natural cells and continue the proliferation, and eventually leading to caspase-independent cell death while the presence of E6 can prevent this. E6 signaling activates mTORC1 to increase protein synthesis even in growth factors absence [14]. MicroRNAs are non-coding single-strand RNAs that regulate the expression of the genes [15, 16]. Their other supervisory functions include reciprocal interaction in initial miRNA transcription, connection to double stranded DNA in order to form Triple-stranded DNA and interaction with DNA G-quadruple structures that interfere in special gene regulatory locations [17]. miRNA length is between 18 to 22 nucleotides and are widely expressed in eukaryotes [18, 19]. miRNAs play an important role in the cancer progression by affecting cancerous cells and their living environment. Almost 30% of genes coding proteins are regulated by miRNAs. About 60% of mammalian mRNAs are targeted by at least one miRNA [20]. Most of the miRNA genes are transcripted by RNA polymerase II in the nucleus. About half of the known miRNA genes live in host genes, and most of them are expressed on the introns of encoding genes [21]. Meta-analysis of recent miRNA profiles in cases of cervical neoplasia and natural cervical epithelium samples has identified 42 cases of upper expression and 21 cases of lower expression during various stages of cervical neoplasia, some of which have been addressed in this paper [22]. The purpose of this paper, is to review the mechanisms of cervical cancer and the events that occur since HPV virus activity in the body begins, and assess the expression of some miRNAs involved in this type of cancer and pathways activated during these mechanisms.

Cervical Cancer Mechanism

Cervical cancer mechanism is a complex pathologic process in which multiplication and apoptosis of cervical cancer cells are regulated through various signaling pathways, including P53 tumor proteins, phosphatase and tension homolog. Cervical cancer is a gradually progressing disease caused by HPV. This type of cancer occurs in lower uterus, where it connects to vagina. Residual HPV infection is the main cause behind cervical cancer [23], but that does not mean all patients with HPV infection will certainly experience the cervical cancer [24]. It is worth noting, HPV is not enough for causing cervical cancer, and not all cases with high risk HPV infection would develop Cervical intraepithelial neoplasia (CIN). Most of the time, the infection is cleared by the immune system, But there are also cases that lead to integration into the host genome, resulting in abnormal structures and functions of genes and cervical cells. [25]. If the HPV infection be stable and lasts for 1 to 20 years, natural cervical tissue, will transform into precancerous lesions including cervical intra-epithelium neoplasia (CIN) I, II, III, and eventually cancer [26]. HPV from the papillomaviridae family, belongs to a class of Small double stranded DNA with no loops with a diameter of 50 to 55 nanometers. Among the 60% HPV genotype that infect the cervicovaginal epithelium, only 12 to 13 types are dangerous and cause cervical cancer [5]. In fact, of the 300 types of known genotypes, only 200 are harmful to humans. Despite that, HPV has been widely accepted as the principal cause of CC and exists in about 100% of tumors [27]. The highest percentage of this disease is of the Squamous-cell carcinoma type and about 10% of that is of the adenocarcinoma type. High levels of squamous cell carcinoma antigen (SCCA) are present in 20% to 60% of the initial CC patients. HPV infection is also more prevalent among HIV-infected women [24]. HPVs are in five types: alpha (HPV 16, 18, 31, 33, …), beta (53 types, including HPV 5, 9, …, 49), Gamma (98 types including HPV 4, 48, 50, …), Mu (3 types including

HPV 63, HPV 1, HPV 204) and Nu (HPV 41); among which, alpha HPV are the most recognized, as they include 5% of cancers. Low-risk types of HPV include HPV-6, 11, 42, 43, 44 and High-risk types consist of HPV-16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70 [28]. These virus types, according to their ability in infecting epithelial cells or internal tissue, are classified into dermal and mucosal subtypes. High-risk HPVs are from the mucosal alpha subtype which are classified as group 1 carcinogens [14]. If the HPV infiltrates cervical epithelium through micro-scratches, HPV infection begins. This is when the expression of E1 and E2 will lead to the regulation of viral multiplication in the infected cells and the expression of initial proteins [24]. HPV infection in the squamous epithelium base layer starts where at first E1 and E2 are responsible for the multiplication of viral DNA in low transcription numbers. When the basal cells are differentiated for forming the epithelial suprabasal layer, viral genome multiplication turn into high transcription number state. Viruses are released after digesting the epithelia and cause infection in the neighborhood cells. HPV genome can combine with the host genome or remain in the episomal form. 83% of cervical cancer cases with positive HPV show the combination of virus genome with the host genome. In case the HPV viral genome merges with the host genome, it will cause interference in the E2 gene location. The E2 gene is in charge of suppressing the E6 and E7 genes; thus viral genome merge causes E6 and E7 to activate in the host genome [14], and E5, E6 and E7 oncoproteins will start to express themselves, helping the cell to stay alive with uncontrolled expansion [29]. Viral oncoproteins such as HPV E6 and HPV E7 have central role in leading the cells towards oncogenesis; during the viral genome multiplication, they can induce all the characteristics of cancerous cells such as, uncontrolled cell expansion, angiogenesis, invasiveness, metastasis, and unlimited telomerase activity, as well as escaping apoptosis and growth inhibition activities [14]. High-risk HPVs contain E6 and E7 oncoproteins which help the appearance of cervical SCC oncogenesis, by turning off inhibitive proteins of Rb tumor, P53 and several cancerous genes [13]. The E6 protein can inhibit the P53 suppressor tumor and prevent its function as a cascade signaling apoptosis via E5AP protein connection. The CDK pl6Lnk4A (Tumor suppressor protein) is one important target of HPV E7 for regulating the cellular cycle [14]. Both E6 and E7 proteins are involved in regulating the cellular cycle and affect the signaling pathways for cellular regeneration and apoptosis. Although P53 activates apoptosis , p-RB functions mostly rely on deactivation of transcription functions such as E2F [13]. The HPV E2 protein is a transcription suppressor for oncogenes. When the HPV merges into the host genome, by suppressing the E2 gene, leads to the production of oncoproteins E6 and E7. E6 attaches to the P53 tumor inhibitor (according to the observations, deactivating the P53 pathway by the HIV infection can stimulate the chemical resistance in cervical cancer by increasing the expression of Mcl-7 and Bcl-2), whereas E7 attaches to the retinoblastoma protein (Rb) suppressor and causes disruption in the cellular regulation cycle, and the uncontrolled cellular multiplication, which increases cellular survival [28]. Viral infection expressed, E7 then connects to p-Rb and inhibits its compound via E2F and helps continuous cellular multiplication [13]. The expression of MHC and TAP-1 class molecules in the HPV-infected cervical cancer tissue is set to be considerably low and the extent of MCP-1 is much lower than stroma around the cancer cells. These immune system adjustment genes are activated via transcription or directly via STAT activated by INF or via IRF-1 caused by INF [30]. The transmembrane protein stimulates INF (STING) genes that recognizes the double strand DNA in cytosol, causing cascade signaling including Kinase-1 (TBK1) and interferon regulatory factor 3 (IRF-3). STING has a fundamental role in inherent immunity, and can be activated via a IFI 16 on a receptor such as AIM2. According to the reports, IFI 16 acts as a DNA viral sensor, that can activate the signaling path STING-TBK-1 for the viral defense [31]. In fact the STING signaling is important in empowering the anti-tumor immunity in different cancers. STING is an endoplasmic network adaptor that can ease innate immunity signaling. In fact, the inherent immunity system is the first line of host defense that can establish Pattern recognition receptors (PRRs) against viral indection; STING is absorbed when multiple viruses and DNAs are activated within the cell, and activates downstream TBK-1 to start a cascade signaling. It thus activates the interferon regulating factor (IRF) and Nf-kb. According to the studies, STING can prevent the progression of cancer [32]. In normal cells, NF-Kb remains hidden and resides in cytoplasm; while after being activated, it is dismantled by the IBK proteins, and its subunits move to the nucleus, where they connect to specific DNA strands and start transcripting and translating them into proteins. If the NF-kb activation is caused by chronic inflammation, the expression of its subunits increase and lead to the translation of uncontrolled protein, causing chronic infection in cancers [33]. In fact the mechanism in which HPV can escape the host immunity supervision, is the deactivating of STAT or IRF-1. When HPV-infection risk is high, E6 and E7 oncoproteins are created (Fig. 1). HPV 16 E6 connects to the carboxyl terminal transactivation domain of IRF-3 and inhibits its transcription without targeting for destruction by proteasome. IRF-3 is part of the transcription factor, activated by the virus, and its activity increases in response to the viral infection and plays a role in the expression IFNI. HPV E7 interferes with IRF-1 which is vital for the INF signaling and cancels its functioning probably via histone Deacetylation [34]. The E6 proteins encoded by HPV cause the proteinogenic activity of STAT3 transcription to increase in the human primary keratinocytes.

Phosphorylation of STAT3 (signal transducer and activator of transcription 3) in cancerous cells with positive HPV, is mostly through automatic activation of keratin via the inflammatory protein interleukin 6. The synthesis of IL-6 is controlled via E6 stimulation from nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signaling, which is dependent upon a signaling pathway which needs GTPase Rac1 and Kinase AKT (Protein kinase B). The transcription factor of NF-kB is an important regulator in the expression of IL-6 which activates in response to a number of outer cell ligands such as TNF-*a* [35]. Tumor necrosis factor-a (TNF-a) plays an important role in a wide array of biologic processes and regulates cellular proliferation, differentiation, and apoptosis (Fig. 1). TNF-a resides in various types of tumors and in addition to the ability to control tumor cell growth and induce tumor necrosis, it causes the tumor cells to multiply, migrate and attack tumor cells [36]. In this case, blocking of antibody IL-6 in positive HPV cell will inhibit STAT3 phospholiration [37]. STAT3 signaling and Viral oncogene expression, controls E6 and E7 during cervical cancer. PD-L1 is a marker on the surface of several cells including tumor cells which help the tumor cells to escape the immune cell protection. According to the literature review, HPV infection is connected to PD-L1 in cervical cancer [38]. The expression of PD-L1 and IFI 16 in the HPV positive cervical cancer increases, and the analysis shows that a removal of IFI 16 reduces PD-L1 and causes an inhibition of multiplication and invasiveness among the cervical cancer cells [39]. As a tumor suppressor, IFI 16 activates the P53 signaling pathway and causes inflammation in some cases of cancer. High-risk HPV (HR-HPV) which includes HPV-16 and HPV-18, controls three oncogenic proteins, namely E6, E7, and E8, together with some interactions in host cells and important agents and signaling pathways for cellular transformation (Similar to E7 and E6, E5 also plays a role in cancer; as this protein is able to increase cellular multiplication by means of interaction with Epidermal growth factor (EFG), thus

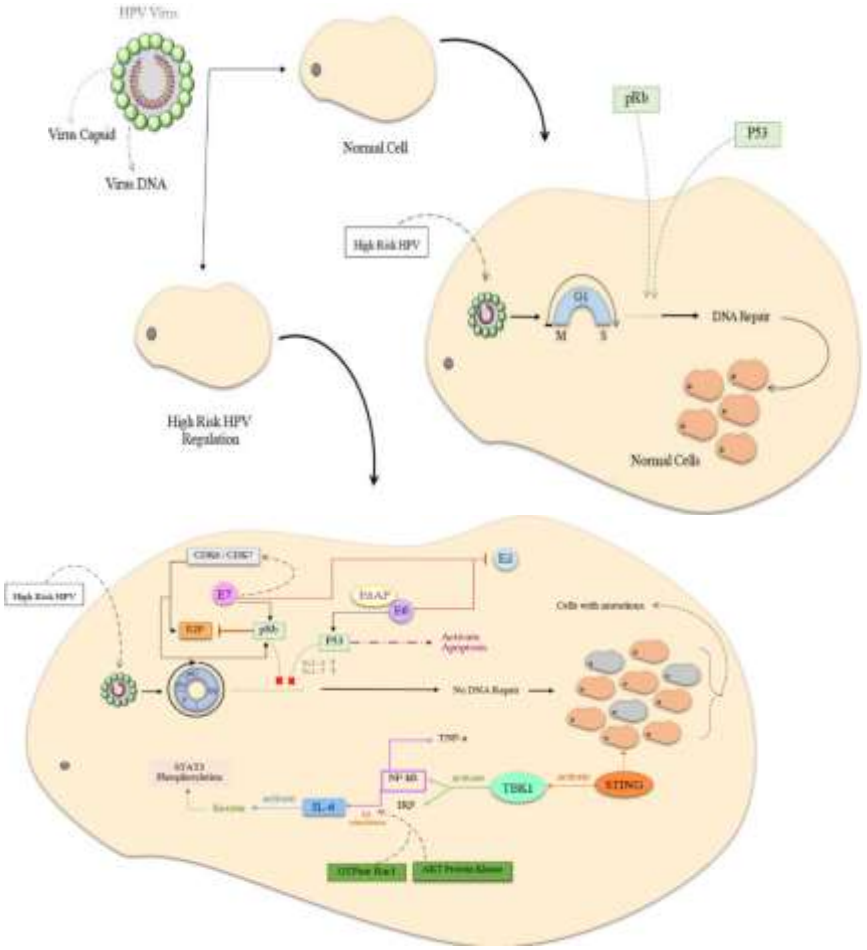

Fig. 1*. The mechanism describing HPV activity inside the body. The entrance of HPV virus into the body is met with reactions aimed at destroying the virus; not all of which are successful in removing the virus by the immune system. After passing the G1 stage, the virus can be destroyed if it is affected by P53 and pRb, and DNA repair is performed to keep the cells healthy. However, if the immune system fails to destroy the cell, P53 and pRb activity is inhibited by the E6 and E7 and they cannot interfere in the growth and multiplication of the cell and with no DNA repair, infected cells are generated and their multiplication continues. Meanwhile STING will start its anti-tumor activity by activating downstream TBK1 and ease the innat immune system signaling, following which IRF and NF-kB (in response to TNF-a) are activated. IL-6 production from NF-kB signaling is controlled by E6 stimulation and GTPaseRac1, and AKT Kinase protein. Among the events that occur with IL-6 activation is the automatic activation of creatine by IL-6 resulting in STAT3 phosphorylation, in which HPV-encoded E6 increases the protonogenic transcriptional activity of STAT3 in primary human keratinocytes. E5 protein is relatively weak in cell transformation and activates EGFR (Epidermal Growth Factor) signaling. EGFR activation is associated with the activity of the viral encoded ion channel (viropurine) E5 [40], While, HPV-16 is the most common type of HPV carcinogen; 50% of uterine cancers are due to HPV-16 [41].*

Helping the progression of tumor [29].

The Role of MicroRNA in Cervical Cancer

Data shows microRNAs play a role in all tumor stages from the beginning to metastasis. Moreover, tumor differentiation stage and microRNA expression in natural and tumor tissues are different and this different expression is related to the origin of the tumor [2]. MicroRNAs, are small endogenous noncoding RNAs that are considered important elements of cancer signaling network and can regulate many of cellular processes such as cellular multiplication, growth, differentiation, programmed cellular death (apoptosis), cell cycle, and tissue growth [42]. They can also suppress protein expression by destroying or inhibiting the translation by attaching to specific zones in mRNAs [43]. microRNAs mostly attach to untranslatable locations (3' or 5') mRNA (UTR) zones of their target and considering their function participate in regulating the translation of proteins or destruction of their mRNAs [44]. 13 types of mRNAs are regulated according to dangerous HPV-16 and HPV-18 strands in the keratinocyte cell species. According to the newly performed studies miRNAs can act as oncogenes by inhibiting endogenous tumor suppressive genes, or as tumor suppressors by suppressing cellular oncogenes [45]. MicroRNAs can act as oncogenes, playing an important role in the progression of cancer by propagating metastasis and regulationg tumor inhibiting genes. Tumor suppressing microRNAs can in general suppress the progression of tumor by targeting mRNAs which code oncoproteins and suppress oncogenic mRNA translation [44]. During initial stages, TGF-B acts as a tumor suppressor, while in advanced stages, it plays an oncogenic role.

TGF-B is a multi-purpose supervisory protein in control of multiplication, differentiation and other functions; According to experiments, high risk HPV E7, regulates TGF-B via E2F and the E2F protein attaches to the promotor of TGF-B gene [45]. The biogenesis of miRNAs are usually regulated via TGF-B; miRNA-128 is expressed in cervical cancer tissue and acts as an OncomiRNA. The change in miRNA-182 occurs along with disruption in cellular multiplication via targeting FOXO1 with cervical cancer pathogenesis [46]. Smad proteins also act as a regulator of maturation in a subset of miRNAs via an smad connector element in promotor in the TGF-B signaling pathway [47]. For example, smd4 is a transcription factor for miRNA-182 [48]. There evidences indicating that TGF-B expression in cervical cancer is above its normal threshold and has been amplified. According to this evidence there is a relationship between HPV and TGF-B existance. Circular RNAs, are non-protein encoding RNAs that can regulate the progression of cervical cancer via the ceRNA network. For example, hsa-circRNA-101996, deactivates the TPX2 function by inhibiting miRNA-8075 causing multiplication and migration of CC [49] (Fig. 2). The discovery of circRNA is mostly by mediation of gene expression in cancer progression via limited competitive regulators, especially miRNAs. Among others, we can mention hsa-circ-0000263, which regulates the miRNA-15005p/MDM4/P53 pathway and inhibits the progression of CC; as well as circ-0067934 which adjusts the miRNA-545/EIF3C axis to stimulate the progression of CC [50]. Previous researches indicate that the

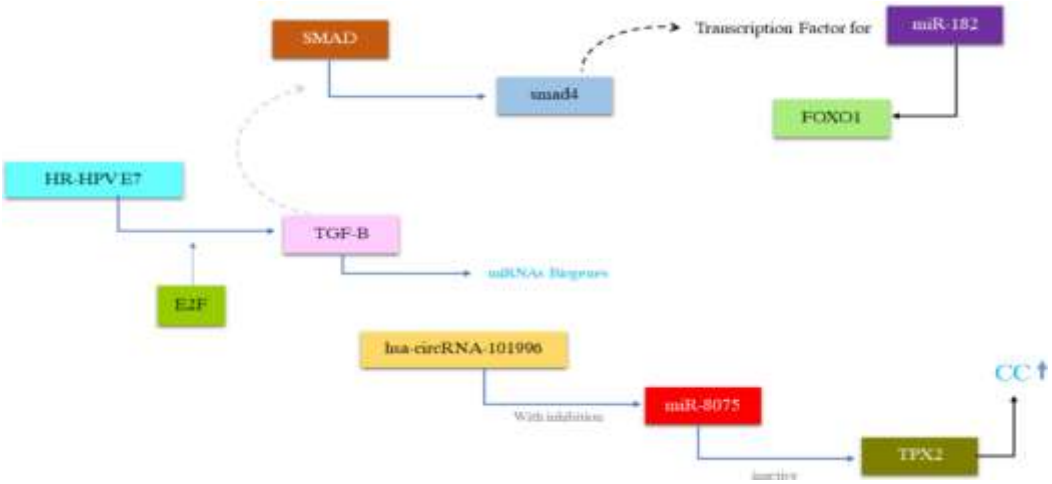

Fig. 2*. The role of miRNAs in cervical cancer. TGF-B regulation occurs via high-risk HPV-E7 aided by E2F. This multipurpose supervising protein causes miRNA biogenesis. For example, miRNA-182 which contains a transcription factor named smad4, causes disruption in cellular multiplication by means of targeting FOXO1 and involves cervical cancer pathogenesis. Moreover, the inhibition of miRNA-8075 happens by deactivating TPX2 via hsa-circRNA-101996 which is followed by an increase in CC.*

expression of circAGFG1 increases in CC, and its silence increases multiplication and migration; in fact, circAGFG1 promotes RAF1 expression via miRNA-370-3P and activates the RAF / MEK / ERK pathway to regulate CC progression.; meaning it propagates the progression of cervical cancer via miRNA-370-3P/RAF1/MEK/ERK signaling [51]. The HR-HPV E5 oncoprotein enhances EGFR ligand-dependent activity, which in turn amplifies signals transmitted through the MAPK / ERK pathway that lead to the expression of genes involved in cell proliferation. [52].

miRNA Reaction Against Cervical Cancer

According to the research legacy, transformed expression of microRNAs is in connection with multiplication, apoptosis and migration of cervical cancer cells. Certain microRNAs such as microRNA-24, microRNA-27b, and microRNA-21 have been identified which are overexpressed in the cervical cancer [53]. miRNA-25, miRNA-378 and miRNA-92a increase with CC cell progression [54]. According to studies, microRNA-29a regulates atherosclerosis, which reveals the existence of a relationship between TNF-a and microRNA [55]. The most common expressed miRNA in most cancers, is microRNA-21; Programmed cell death (PCD) is a target for miRNA-21, and its overexpression can lead to an increase in cellular multiplication in cervical cancer HeLa cell species [56]. This microRNA can be used as a marker to detect cervical cancer metastasis. miRNA-21 expression is aided by AP-1 activation in cervical cancer cells. According to research legacy, the AP-1 transcription factor family members including C-FOS and C-Jun are important in regulating the miR-21 gene in cervical cancer cells with high-risk oncogenic HPVs. AP-1 is a transcription factor in the expression of pathophysiological responses, including cancer. Among the signaling pathways in modulating the activity of this factor in response to external stimuli, various MAPKs such as ERK, JNK and kinase P38 can be mentioned. [57]. The expression level of TNF-a is correlated with the expression level of microRNA; according to experiments; high or low adjustment of TNF-a respectively lead to amplification or inhibition of cervical cell multiplication, with no effect on apoptosis of cervical cancerous cells. Therefore, TNF-a/microRNA21 signaling has a supervisory role in the multiplication of cervical cancer cells [23]. Moreover, the expression of miRNA-21 is accompanied by HPV infection and it gradually increases in natural cells, cervicitis and SCC-Ag. The unadjusted level of miRNA-21 is related to the increase in the expression of IL-6 which may have a role in inflammatory processes. miRNA-21 adjustment can inhibit CC by means of inhibiting PTEN [58]. According to conducted studies, miR-29 targets the gene associated with HPV.

The expression of miR-29 with TGFB which is a highlighted EMT factor, has the opposite relationship. In fact, its expression will directly lead to TGFB1 and TGFB2 suppression and inhibits the expression of ECM proteins. According to the information, miR-29a is adjusted through a signal transducer and activator of transcription 3 (STAT3), and miRNA46a inhibition adjusts the immune antitumor response along with several cytokines [59]. The low level of miRNA-22 expression is correlated to increase in survival among patients suffering CC, and the inhibition of tumor growth have been observed via targeting ATP citrate liase by these miRNAs [60]. miR-22-3p causes an adjustment in the growth of cervical cancerous cells and plays an important role in the progression of this cancer. The connector protein family elF4E and the MAPK signaling pathway, have the highest correlation with this miRNA. elF4EBP3 gene is the direct target of the miR-22-3p. The direct target of miR-22-3p is the elF4EBP3 gene, which is suppressed by overexpression of miR-22-3p. [61]. A decrease in the expression level of miRNA-218 in the serum, is similar to samples of CC tissue and the level of this miRNA is correlated to the tumor stage in patients [62]. An increase in the level of miRNA-205 in the serum is correlated to CC tumor stage and reduces the rate of survival among patients [63]. A reduction in the expression of miRNA-218 level in the serum, is similar to the CC tissue samples and the level of these miRNAs is correlated with the stage of tumor in patients [62]. An increase in the level of miRNA-205 in serum is related to cc tumor stage and reduces the patient's survival [63]. miR-200a can simultaneously target several genes that are important for the metastatic potential of cervical cancer cells. Studies have shown that the miRNA family may prevent epithelial-to-mesenchymal transition (one of the most important steps in initiating tumor metastasis) by targeting the ZEB2 and ZEB1 E-Cadherin transcription suppressors. Transforming growth factor B_2 (TGFB2) is among the targets of this miRNAs, causing the propagation of metastasis in several types of cancer. By this way miRNAs can act as the main suppressor of cervical cancer. In fact, cervical cellular stimulation decreases significantly in time of miR-200a expression [64]. miRNA-27b in cervical cancer cells and tissues is adjusted in an interesting manner. Overexpression of this miRNA in tissues and cervical cancerous cells leads to the inhibition of CDH11 (Cadherin 11) and the increase of cervical cancerous cells, as well as the inhibition of cellular apoptosis caused by paclitaxel through PLK-2 expression reduction. NHE1 is an oncogenic factor and a downstream molecule from PPARy. PPARy causes a reduction in the expression of NHE1 in cervical cancer and in this regard, it acts as a tumor suppressor in the cervical cancer. This inhibitor, is a direct target of miR-27b. In the end miR-27b causes BRC and cervical cancer

tumorogenesis [65]. The target for the miR1246 is THBS2 (thrombospondin-2) gene which adjusts cellular migration through extracellular matrix hydrolysis. This gene can also play a significant role in the inhibition of angiogenesis through the adjustment of matrix metalloproteinases (MMPs) and ECM proteins. Low expression of miR-1246, inhibits the growth of tumor and disrupts the invasion of cervical cancerous cells. In fact, low expression of this miRNA will lead to increased expression of THBS2 and redued expression of MMP2 and MMP9 [66]. The WNT/B-Catenin signaling pathway is adjusted negatively by HMGB3. In fact, miR758 adjusts tis signaling pathway via HMGB3. MiR758 will prevent the multiplication of CC cells by HMGB3.In fact, the miR-758 regulates this signaling pathway through HMGB3. MiR-758 inhibits CC cell proliferation by HMGB3. Overexpression of HMGB3 increases the expression of B-Catenin, C-Myc and MMP7 and is decreased in protein and mRNA levels by miR-758 [67]. Table 1 introduces

Table 1. *Down/up-gulated particular microRNAs and correlated signaling pathways which mediate the cervical cancer*

MicroRNA in CC	Regulation	Canonical Pathway	References
miR-877	Downregulated	MACC1	[68]
miR-449a	Downregulated	G6PD	[69]
miR-758	Downregulated	HMGB3 through the WNT/B catenin signaling	[67]
miR-432	Downregulated	FN1	[70]
miR-134	Downregulated	NCK1-AS1 gene	[71]
miR-216b	Upregulated	FOXM1 gene	[72]
miR-1246	Downregulated	Thrombospondin-2	[66]
miR-889	Downregulated	FGFR2	[73]
miR-215-3p	Downregulated	SOX9	[74]
miR-27a	Upregulated	INNP1	[75]
miR-22-3p	Upregulated	MAPK signaling, eIF4E binding pro family, PI3-K/AKT signaling	[61]
miR-214	Downregulated	EZH2	[76]
miR-21	Upregulated	AP-1	[53]
miR-196a	Upregulated	FOXO1 & p27 kip1	[77]
miR-23b	Downregulated	Six1-AKT/mTOR Signaling	[78]
miR-425-5p	Upregulated	AIFM1	[79]
miR-217	Downregulated	ROCK1	[78]
miR-27b	Upregulated	Cytochrome P450	[65]
miR-200a	Downregulated	TGFB2	[64]
miR-92a	Upregulated	FBXW7	[80]
miR-378	Upregulated	ST7L/Wnt/B-Catenin	[81]
miR-218	Downregulated	LAMB3	[82]
miR-130a	Upregulated	TIMP2	[83]
MiR-29a	Downregulated	HSP47	[13]

some of these miRNAs, together with their targets.

Conclusion

Cervical cancer is one of the most common types of cancer in women, especially women in low- and middle-income countries, whose main cause is infection with the high-risk HPV virus. There are oncoproteins that begin to function with the onset of HPV infection, each of which plays a role, including oncoprotein E6, which inhibits p53 function, and oncoprotein E7, which disrupts pRB function. Studies have shown that there is a link between some miRNAs and cervical cancer. As cancer progresses, the expression and function of these miRNAs change, the most common of which is miRNA-21, and its expression increases in the conventional AP-1 pathway, one of its targets is PCDP4. Other cases include TNF-α expression levels. In fact, high regulation of TNF-a enhances the proliferation of cervical cells and low regulation of it inhibits the proliferation of these cells, while this factor has no role in the apoptosis of cervical cancer cells. It is expected that in the near future, new methods will be used to predict and prevent the progression of this disease and ultimately treat people, and the use of miRNAs will definitely have a special place in this way.

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How to cite to this article: Soleymani A, Alibalazadeh Yamchlou N, Jalili A, Ebrahimi Sadrabadi A. The Regulatory Role of Differential Expressed MicroRNAs and Viral Oncoproteins in Angiogenesis of Human Papillomavirus-Related Cancer. Mod Med Lab J. 2020; 3 (2): 88-99