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PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

OPEN ACCESS Pakistan Journal of Biological Sciences

ISSN 1028-8880
DOI: 10.3923/pjbs.2020.977.988

Review Article
Human Papillomavirus, MicroRNA and their Role in Cervical Cancer Progression, Diagnosis and Treatment Response: A Comprehensive Review

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Abstract

Human Papillomavirus (HPV) is sexually transmitted and linked with vaginal, vulvar and cervix cancers in females, penile cancer in male, while anal and oropharyngeal cancer in both genders. Cervical cancer is ranked as third most identified cancer among females globally and is the fourth leading reason of cancer related mortality. The main aim of current study is to highlight the key role of miRNA in cervical cancer development, progression and their therapeutic responses. Current study entailed more than 50 PubMed cited articles related to miRNA role in cervical cancer. Studies have elucidated the role of miRNAs regulation in gene expression at post-transcriptional and translational level by targeting significant genes and therefore involved in cervical cancer. miRNAs control several cellular pathways involved in development of pre-malignant to metastatic stage and proliferation to malignancy. Current review elucidated and elaborated the key role of miRNA their application, treatment and therapeutic responses in cervical cancer.

Key words: Cervical cancer, gene expression, cancer biomarkers, neoplasia, mortality

Citation: Adil Jamal, Imran Shahid, Muhammad Naveed Shahid, Mohammed Saleh Alshmemri and Fayez Saeed Bahwerth, 2020. Human papillomavirus, MicroRNA and their role in cervical cancer progression, diagnosis and treatment response: A comprehensive review. Pak. J. Biol. Sci., 23: 977-988.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Human Papillomaviruses (HPV) is associated with different cancers like vaginal, cervical and vulvar in females, penile cancer in male while anal and oropharyngeal cancer in both genders[1-3]. Cervical precancerous lesions including Cervical Intraepithelial Neoplasia (CIN) grade 2 and grade 3 arise by HPV infection. Depending upon the viruses proliferation ability of infected cells leading to malignant transformations, HPVs can be further classified as low, intermediate and high risk oncogenic potentials[3,4]. Low risk HPVs comprise HPV 6, 11, 42, 43 and 44 may account benign cervical lesion with no malignancies formation[3,5,6]. Intermediate oncogenic risk HPVs comprise types 31, 33, 35, 51 and 52 with no demarcation of malignant transformations[7,8]. Neoplastic transformations arise through the high oncogenic potentials including HPV types 16, 18, 45 and 56[7,8]. Current study will highlight and broaden the horizon and key understanding about the principal role of microRNA in cervical cancer progression, development, clinical utility and treatment responses.

HPV GENOME AND ITS TRANSMISSION

The HPV, non-enveloped viruses belong to family papillomaviridae with sturdy resemblance to polyoma viruses. The HPV are circular double stranded DNA, non-enveloped icosahedral capsid. The HPV genome consists of three regions; early, late and genomic regions. Early regions E1, E2, E4-E8 comprise half of genome. E1 and E2 do DNA replication and RNA transcription, respectively. E4 performs cytoskeleton reorganization and E5-E7 executes cell transformation (Table 1). Late region consist of L1 and L2 form structural component of viral capsid constituting 40% of genome. Mucosal epithelial cells or basal layer of epidermal is region for HPV multiplication and proliferation. HPV has strong ability to infect either by non-sexual (oral mucosa, skin) or by sexual (anogenital). Mostly HPVs transmission is through sexual means including rectal and vaginal sex. Important risk factors in HPV transmission include number and age of sex partners, male circumcision and smoking[12]. In oral HPV infection, oral sex are main factors of HPV transmission. Perinatal transmission of HPV from mother to fetus occurs along other viral and microbial infections[13,14]. Immunologic responses clear the most of HPV infections by 6-12 months after appearance.

Global impact of HPV in cancers: HPV, so far is the most common sexually viral transmitted disease. During the life time, HPV affects 50% adult population[15]. The highest HPV prevalence rate is seen in South Africa (24%) followed by Eastern Europe (21%) and Latin America (16%)[2]. Cervical cancer indicated highest HPV prevalence of 85-99% globally[2]. Different genotypes of HPV causes both cancerous and non-cancerous diseases. Skin warts, respiratory tract, throat, oral mucosa and genitals have been associated with HPV infections. Higher genital HPV infections have been reported as that of oral HPV. Globally, 50% of HPV based cancers in female and 5% in men are associated with HPV infections[16,17]. Genital HPV infections displayed more than 99% cervical cancers[1], anal cancer (97%)[18], penile cancers (47%)[19], vulvar cancers (40%)[20], oropharynx cancers (47%) and oral cavity cancers (11%)[21].

HPV role in cancer progression: Cancer development and its progression is not very well known in patients with HPV infection. Several hypothesis stated the HPV routes towards cancer development. One hypothesis stated that metastasis risk is higher due to increased proliferation of the basal layer at metaplastic epithelial sites at the time of puberty and sexual activity[22]. The primary infection of cell and its link to disease development is not very well explained. Broadly, HPV infection induces cell destruction besides cell transformation. The HPV hamper cell cycle control and avert apoptosis with spontaneous DNA replication. Another hypothesis stated that laminated epithelial layer of transformation zone developed through squamous columnar annexation with cervix maturity, like epithelial basal cells[23]. It is assumed that lesion development initiated with the basal stem cell infection and persistent lesion relies on endurance of stem cell[24]. HPV low risk types do not precede to neoplasm and do not markedly arouse the basal cell multiplication. One hypothesis proposed the E2 probably involved in genome partitioning and E2

Table 1: HPV proteins and their functions

HPV proteins	Function
E1	DNA replication[9]
E2	Viral RNA transcription regulation, cell transformation, regulation of apoptosis[9]
E4	Cell cycle regulation, alteration in formation of HPV-1 provoked nodules[10]
E5	Viral DNA transformation, maintenance of viral replication and proliferation, Infection prevention apoptosis[9]
E6	Inhibition of tumor suppressor activity of P53[11]
E7	Malignant transformation of infected cells via destructing cell cycle, Inhibition of tumor suppressor activity of RB[11]

modulation in viral transcription[25]. Among all the HPV viral proteins, E6 and E7 are principally correlated with cancers arising anti-apoptosis, genetic alteration and dermal or mucosa lesion development by inhibiting the tumor suppressors Rb and P53[26,27]. Viral protein E6 and E7 their function differs between low and high risk HPV types that are associated with varied infections[28]. HPV E7 protein of high risk types target and degrade RB1 while E6 proteins stimulate telomerase (TERT) by targeting TP53. Hence for high risk HPV types based cell immortalization *in vitro*, initial stage is accomplished by telomerase activation[29]. Modulated expression of p16-INK4a is thought to be associated with HPV oncogenesis mechanism. High risk HPV E7 protein, suppresses CDK4/6 through p16-INK4a, RB1 mediated cell cycle arrest and thus senescence happens by provoking p16-INK4a via KDM6B histone demethylase[30-32]. More genetic aberrations including chromosome lagging, multipolar spindles, abnormal centromeres and chromatin anaphase bridges are noticed in cells with HPV16 E6 and E7 genes[33]. At early stages of HPV infection, these genetic changes occur in cell, but they can be recognized incontestably in invasive cancers.

GENITAL TRACT AND CERVICAL NEOPLASIAS

Genital tract neoplasia include vaginal, cervical and intraepithelial regions and portion of these progress to invasive cancers[16]. HPVs life cycle control is very well known in lower genital tract neoplasias[34,35]. In 90% cervical cancers cases, most predominant type is HPV16[36]. Only 10% of cervical cancer are adenocarcinoma usually incited by HPV infections[16]. The risk factors in cervical cancers meet the same criterion as that of general HPV infections like use of hormonal contraceptive, earlier ages pregnancy (18 years old or earlier) and high parity[36]. Different other factors also contributed in progression of cervical cancers like co-infection with Sexually Transmitted Diseases (STDs) like HIV, herpes simplex virus and immune suppression[1,36]. In HPV associated cervical cancers, HPV proteins E6 and E7 are supposed to perform their role during disease progression[37]. About 35% HPV induced cervical cancers are believed due to E2 gene[38]. When viral DNA integrates into cell chromosomes, the gene expression regulation is altered. This results in uninterrupted expression of E6 and E7 proteins inducing mutations accumulation and developing malignancies[33]. Aggregation of mutations predominantly structural variations, monosomies, trisomies, breaks and gaps in chromatids are often identified in cervical cancers.

The CIN1 progression mechanism leading to CIN2 and CIN3 is not well understood, it might be due to improper regulation (dysregulation) of viral gene expression or initial integration events in CIN1. Instability of chromosomes resulting into integration might be due to early deregulation. Dysregulation and altered expression of E6 and E7 proceeds to high grade lesion such as; CIN2 and CIN[39]. In this pattern, flat warts showed resemblance to CIN1 lesion, yet in basal and parabasal portions cell proliferation is low level[6]. In high risk HPV types, E6 and E7 viral protein expression increases resulting into CIN2+ phenotypes. This type of phenotype leads genetic modification culminating towards cancer development. The other lower genital neoplasias include vaginal and vulvar cancers. Squamous Cell Carcinomas (SCC) induced vulvar and vaginal cancers[22]. HPV16 (54%) type is detected in majority of vaginal cancers followed by HPV 18 (8%)[22]. Vulvar cancer represents about 4% of all neoplasms of the female genital tract[40]. HPV16 and HPV18 is associated with 32 and 4% cases, respectively[41,42]. In both vaginal and vulvar intraepithelial neoplasia, HPV DNA is detected however only half of these neoplasias cause cancers.

Penile and anal carcinoma: Squamous epithelium of the glans, penile foreskin inner surface, coronal sulcus are areas where penile carcinoma originate. Squamous Cell Carcinomas (SCC) are uncommon and generally occur in uncircumcised male[42]. High risk HPV infection are related to half (40-50%) penile SCC[43]. Principally, HPV16 and HPV18 contributed 69 and 1% penile SCC, respectively[22]. High risk HPV types, usually HPV16 and HPV18 cause genital warts similar to Bowenoid papulosis with high grade SCC *in situ*, present on perineum and external genitalia[44]. Low risk HPVs, HPV 6 and HPV 11 are related to Buschke-Lowenstein tumors located on vulva, prepuce, penile glans, perianal sites and vagina[45]. HPV16 (75%) and HPV18 (3%) account most of the anal cancers cases[46]. Around 85-95% of anal cancers in both genders reveal HPV DNA positive[2].

Bladder cancer: The HPV infection prevalence varies from 0-81% in bladder carcinomas[47]. Broadly speaking; involvement of bladder cancer is not very well understood. Few studies reported the involvement of E6 and E7 proteins in HPV infection[48] while others reported no connection between HPV infection and bladder carcinoma[49]. Additionally, inactivation and inhibition of Rb protein with involvement of p16-INK4a in HPV infected bladder can lead to progression of bladder cancer[50]. Contradiction prevails so far with

inverted papilloma of urothelial[51,52] and urinary bladder carcinomas[53], but in others no association was reported[54].

HPV in non-oncogenic diseases: HPV diseases besides neoplasia include the genital, common, filiform and flat warts[55]. Low risk HPV types HPV6 (89%) and HPV11 (11%), even both low and high risk HPV types probably cause genital warts[56]. Another type of flat warts, condylomata plana are related to HPV infection[57]. Even after three months one third of individuals having recurrence of genital warts with lesions development[58].

miRNA AND THEIR ROLE IN CARCINOGENESIS

miRNAs are highly conserved, endogenous short (17-22 nucleotides) non-coding RNAs. miRNAs regulate gene expression by performing RNA cleavage or by suppressing mRNA translation and have key role in developmental processes[59]. The miRNA processing usually initiated at transcription stage by RNA polymerase II to primary RNA (pri-miRNA). This pri-miRNA is sliced into pre-miRNA by nuclear RNase III Drosha and the ultimately converted by Dicer another RNase III to mature miRNA. The miRNA attach in the 3 untranslated region (UTR) of target mRNA with complementary sequences which inhibits translation, enhance the degradation of target and further modifies gene expression regulation. The miRNA suppresses the translation of target genes that results in blockage of eukaryotic Initiation Factors (eIF) through its binding to mRNA via recognition of 5 tail cap structure of the mRNA. Poly A binding protein attaches to mRNA at 3 poly A tail to bring eIF4G to mRNA and hence, translation initiates by combined action of the mRNA cap structure and poly A tail.

The miRNAs regulate 60% of protein coding gene leading to regulation of cell processes. The miRNAs those with modified expression pattern they have been recognized in tumor inhibition (anti-oncomirs) or found as oncogenic (oncomirs) in several malignancies. Generally, altered miRNA expression pattern proceed to disturbance in tumor inhibiting proteins and oncogenic levels which later on modifies cell growth by arising tumor malignancy[60]. Broadly, the dysregulation of miRNA in nearly all sort of malignancies is very well understood, as their association during disease onset and progression at every stage[61]. Therefore, miRNAs are appropriate predictive biomarkers candidates and applicable targets during treatment[62].

DIAGNOSIS OF CERVICAL CANCER, LYMPH NODE METASTASIS USING miRNAs

RNases degrade the RNAs immediately while transferred in the blood. Hence, initially it was thought that miRNAs were not present in serum rather those present within cells have been used for expression profiling. However, secreted form of miRNAs found in breast milk and placenta play role in cell transfection via intracellular transmission[63] and in signaling[64]. Extracellular secreted form of miRNA is of considerable importance in cancer prognosis and therapy because secreted miRNAs profile vary between cancer patients and normal. Alterations in miRNAs expression have revealed them as promising biomarker during cancer[65]. The miR34, miR34a, miR-21 and miR-27a showed significantly higher expression in SCC of cervix[66]. Several miRNAs have been recognized as biomarker for LNM. The miR-20a and miR-203 had markedly higher expression in CC patients than normal; however, LNM was found with inhibited expression of miR-203[67]. Another study performed in LNM patients exhibited that miR-20a, miR1246, miR2392, miR3147, miR3162-5p and miR-4484 used as biomarkers for prognosis of LNM[68]. These studies suggested that miRNAs screening can be useful for recognition of LNM in initial CC. Similarly, miR-124 undergoes epigenetic modifications like aberrant hypermethylation in CC[69].

miRNA ASSOCIATION IN CERVICAL CARCINOGENESIS AND CANCER PROGRESSION

Multiple factors proceed Cervical Carcinogenesis (CC) development, encompassing environmental, viral and host dependent elements, which incited malignant growth, invasion and metastasis. Over the last two decades, epigenetic regulation modes highlighted and focused on dysregulation of tumor suppressor genes and oncogenes. The miRNA are well known to play their role during cell cycle progression, apoptosis, metastasis and both radio and chemo resistance[70]. Studies conducted in past reported many dysregulated miRNAs that target those genes which are involved in CC development and progression[71-100] (Table 2). Findings highlighted that miR-21 triggered cell proliferation in HeLa cells whereas its suppression inhibited cell multiplication by enhanced expression of tumor inhibitor gene PDCD4, an apoptotic protein. Later, it was determined that miR-21 a key oncogenic is upregulated in multiple cancers including CC[100]. The miR-886-5p expression profiling revealed its over expression in non-tumor tissues and SCC. *In vitro* assays

Table 2: Differential regulation of miRNA in CC vs. normal sample

miRNA*	Target gene	References	miRNA**	Target gene	References
miR-99a/99b	mTOR	Wang *et al.*[71]	miR-155	LKB1	Lao *et al.*[86]
miR-506	GLI3	Wen *et al.*[72]	miR-196a	HOXC8	Villegas-Ruiz *et al.*[87]
miR-129-5p	SP1	Zhang *et al.*[73]	miR-31	ARID1A	Wang *et al.*[88]
miR-99	TRIB2	Xin *et al.*[74]	miR-130a	Dicer	He *et al.*[89]
miR-203	VEGFA	Zhu *et al.*[75]	miR-215	Not identified	Liang *et al.*[90]
miR-23b	uPA	Yeung *et al.*[76]	miR-125b	BAK1	Wang *et al.*[91]
miR-214	Plexin-B1	Qiang *et al.*[77]	miR-886-5p	BAX	Li *et al.*[92]
miR-497	IGF-1R	Luo *et al.*[78]	miR-944	HECW2/S100PB	Xie *et al.*[93]
miR-214	BCL2L2	Wang *et al.*[79]	miR-205	CYR61/CGF	Xie *et al.*[94]
miR-155	EGF	Lei *et al.*[80]	miR-10a	CHL1	Long *et al.*[95]
miR-302-367	AKT1	Cai *et al.*[81]	miR-19a/19b	CUL5	Xu *et al.*[96]
miR-424	CHK1	Xu *et al.*[82]	miR-20a	TNKS2	Kang *et al.*[97]
miR-17-5p	TP53INP1	Wei *et al.*[83]	miR-133b	MST2/CDC42/RHOA	Qin *et al.*[98]
miR-125b	PIK3CD	Cui *et al.*[84]	miR-21	CCL20	Yao and Lin[99]
miR-143	BCL-2	Liu *et al.*[85]	miR-21	PDCD4	Wang *et al.*[100]

*: Downregulated, **: Upregulated, CC: Cervical carcinoma

Table 3: miRNAs involved in cervical neoplasia development

miRNA	Cellular process	Target gene	Clinical relevance	References
Up-regulated				
miR-886-5p	Cell transformation and progression	BAX	ANTT*, CSCC***	Li *et al.*[92]
miR-10a, miR-96a, miR-132	Cell transformation and progression	HOX	Normal*, CIN***, CIN III***, carcinoma***	Pereira *et al.*[101]
miR-148a	Tumor inhibitor genes	PTEN, P53INP1, TP53INP2	Normal*, CIN and CINIII**, carcinoma***	Pereira *et al.*[101]
Down-regulated				
miR-99a, miR-513, miR-29a	Cell death, tissue development, apoptosis	IGF-1, BCL2L2, VEGFA and CDK6	Normal*, CIN#, CIN III#, carcinoma#	Pereira *et al.*[101]
miR-145	Cell movement	IGF-1,	Normal*, CIN#, CIN III#, carcinoma#	Pereira *et al.*[101]
miR-143	Cell growth, development and proliferation	PPAR signaling	Normal*, CIN##, CIN III##, carcinoma##	Pereira *et al.*[101]
miR-372	Cell growth	CDK2, cyclin A1	Cervical normal tissue→cervical cancer tissue	Tian *et al.*[102]
miR-218	Focal adhesion	LAMB3	CIN III#, CaCu###	Martinez *et al.*[103]
miR-34a	p53-dependent pathway	NOTCH, P18Ink4c, CDK4, CDK6, cyclin A, E2, E2F1, BCL2,	CIN I#, CIN II##, CIN III###	Li *et al.*[104]
miR-100	Cell growth, apoptosis	PLK1	Normal*, CIN#, CIN#, carcinoma##	Li *et al.*[105]

*Low up-regulated, **Moderately up-regulated, ***Highly up-regulated, #Low down-regulated, ##Moderately down-regulated, ###Highly down-regulated

performed on miR-886-5p showed the decreased expression of BAX resulted into reduced apoptosis and increased cell proliferation. Contrarily, knock down of miR-886-5p enhanced the BAX pro-apoptotic protein persuading towards apoptosis[92]. The above mentioned reports manifested miRNAs key role in CC progression.

Principal mechanism of CC development is based upon the differentiating epithelial cells proliferation and involvement of several miRNAs. Different miRNA are attributed to development of premalignant lesions to invasive cancers[92,101-104] (Table 3). High risk HPV, HPV 16 gene sequences are associated with CC development, moderate and severe dysplasia, Invasive SCC because of variable miRNA expression pattern. Reports elucidated the variable expression pattern of different miRNAs in neoplasias and dysplasia (Table 3). These miRNA can significantly use to identify cervical cancer vs normal tissue[101]. An interesting study examined that PLK1, kinase based activity gene engaged in cell cycle transition at G2/M stage lost its function by deregulation of miR-100[105].

Low to high grades CIN and CC tissue showed the gradually declined miRNA expression with increased PLK1 expression in CIN3 tissues. Altered miRNA expression level provoke dysregulated cell cycle, increased cell proliferation and decreased apoptosis[106]. A study performed on 875 human miRNAs disclosed differentially regulated 31 unique miRNAs, of which 14 were up regulated and 17 were over expressed. Among these, miRNA-29 was up regulated, while miR-218 was significantly down regulated. Additionally, miR-29 unveiled the negative interaction between CDK6 and YY1 expression. Expression level of miR-29 was controlled by HR-HPV E6/E7[106]. Another study disclosed that p18Ink4c, a key regulatory element of cell cycle regulation also suppresses the expression of miR-34a and 5 UTR of p18Ink4c. These studies implicated miR-4a downregulation in infected cervical tissues due to continuous p18Ink4c activation[107]. A study performed on 70 differentially regulated miRNAs between normal tissues and primary invasive SCC exhibited 68 up regulated and 2 down-regulated miRNAs. Among these differentially regulated miRNAs, 10 miRNAs were remarkably up-regulated i.e., miR-9,

miR-127, miR-133a, miR133b, miR-145, miR199a, miR199b, miR-199s and miR-214 and only two were down-regulated i.e., miR-149 and miR-203. Moreover, miR-127 expression showed association with lymph node invasion and LNM while reduced expression of miR-199a showed decreased cell growth[108].

miRNAs IN CERVICAL CARCINOMA TREATMENT AND OUTCOME

Anti-cancer therapy can be achieved by regulation of miRNAs expression. This can be attained by overexpression of oncomiRs by applying complementary gene sequences or by inhibiting the actual gene expression. Contrarily, addition of miRNA itself can improve the tumor suppressor miRs with decreased expression in carcinoma. Both methodology are based upon the drugs involving synthetic nucleic acid via transformation system. A transformation system is needed to assure *in vivo* stabilization and precisely introduce nucleic acids containing drugs into cells. One approach for over expressed miRNA in cancer is to suppress the miRNA role using those agents that bind to the miRNA. Overall it looks challenging to apply siRNA for miRNA suppression due to less nucleotides. So, antisense miRNA oligonucleotides (AMOs) are the usual miRNA suppressors. The AMO approach involving drug administration is an effective technique for stabilization and transformation using several modifications. For miR-21, an oncomiR was designed as modified antisense agent in CC. After introduction of this AMO in CC cells, its decreased expression reported suppressed tumor growth[109].

The classical therapy for CC patients comprised radiological procedures coupled with cisplatin. Even though around 50% of patients those who undergo radiotherapy have disease recurrence due to survival of radiotherapy resistant cells within the neoplasm. Hence, radio and chemo-resistance inhibit effective CC treatment[110]. The miRNAs control expression of different targets hence displayed their ability as biomarkers in clinical prognosis. Another study performed on 96 cancer related miRNAs expression analysis unveiled that miR-9 and miR-200a were significantly associated with Overall Survival (OS). Transfection of these miRNAs showed that miR-200a controlled TGFB2, EXOC5, ZEB1 and ZEB2. miRNA-9 controlled the genes involved in metabolic processes, highlighting increased metabolic rate in tumor cells, a prominent character of the rapid multiplication of CC[111]. Expression profiling study of miR-200a and miR-93 in patients with invasive CC and undergoing hysterectomy for benign tissue showed an overexpression of MMP2 and MMP9 targets, while inhibited expression of RECK in CC tissue in benign lesion. RECK and miRNAs expression act as significant predictive markers about survival period in CC patients[112]. In another study, advanced FIGO stage cervical cancer patients, miR-224 was overexpressed in less differentiated tumors and LNM positive patients. Higher expression of miR-224 displayed shorter OS. Higher expression was linked with poor prediction and can utilize as biomarker for prognosis in clinical outcome[113] (Table 4). Another miRNA, miR-26a play key role in CC pathogenesis and suggested it may be used as a potential novel therapeutic strategy for cervical cancer[114]. Another study was performed on 30 miRNAs related to tumor metastasis with radical hysterectomy. Expression profiling studies conducted showed that seven miRNAs i.e., miR-10b, miR-100, miR-125b, miR-143, miR-145 and let-7c were highly suppressed in late stage of SCC as that of early stage SCC patients. Besides miR-10b, others miRNAs were significantly linked with lymph node metastasis and poor survival in SCC. The miR-100 and miR-125b envisaged significant trend towards poor prediction due to decreased expression[115] (Table 4). The aforementioned studies disclosed that miRNAs act as biomarkers of OS, because they modulate genes involved in different functions like transformation, invasion, growth and metastasis.

To understand the complexity and association of miRNAs and the cell processes, 7 miRNAs i.e, miR-9, miR-93, miR125b,

Table 4: miRNA involved in CC clinical outcome

miRNA	Target gene	Function	CC cell type	References
Up-regulated				
miR-93, miR-200a	RECK	Invasion and lymphatic metastasis	Invasive carcinoma	Wang *et al.*[112]
miR-224	Unknown	Intrusive progression	IC	Shen *et al.*[113]
Down-regulated				
miR-9	Unknown	Invasion and cell movement	Small cell carcinoma	Hu *et al.*[111]
miR-26a	PRL-1	Suppress cell proliferation and invasion	IC	Dong *et al.*[114]
miR-100	RSP3, PLK1	Lymph node metastasis	SCC	Huang *et al.*[115]
miR-125b	BAK1	LNM	SCC	Huang *et al.*[115]
miR-143	BCL2, KRAS, DNMT3A	LNM	SCC	Huang *et al.*[115]
miR-145	STAT1, C-MYC, BNIP3	LNM	SCC	Huang *et al.*[115]
miR-199a-5p	SNF, SW1, PAK4	LNM	SCC	Huang *et al.*[115]
Let-7c	HMGA2	LNM	SCC	Huang *et al.*[115]

LNM: Lymph node metastasis, IC: Invasive carcinoma, SCC: Small cell carcinoma, All above mentioned miRNAs have poor survival

miR143, miR145, miR-199a-5p and miR-200a have interaction among themselves and involved in clinical prognosis[116]. The miRNAs were reported unique therapeutic targets[117,118]. The miR-145 regulation in HPV CC cells was controlled by p53 via glucocorticoids. The miR-145 inhibited expression in CC tissues through glucocorticoids action later influenced p53 inhibition and HPV-E6 expression in CC cells. Down-regulation of miR-145 along glucocorticoids decreased the chemotherapy based apoptosis while its up-regulation increased sensitivity to mitomycin and cortisol induced the reverse chemo-resistance. Overall study highlighted the role of miR-145 as target for CC therapy[119]. Twenty miRNAs were differentially expressed in an expression profile of radio resistance cells vs. their controls. Out of these 20, 14 miRNAs were up regulated while 6 were down regulated in CC radio resistant cells. The miR-630, miR-1246, miR-1290 and miR-3138 showed five-fold higher expression in radio resistant cells. Further analysis releveled the upregulated expression of four miRNAs in CC radiation treated cells. These miRNAs showed remarkably enhanced survival rate of radiotherapy treated CC cells. Significant inhibition of miR-630 reversed the radio resistance of CC cells[120]. Another miRNA and miR-214 suppresses cell growth, transformation and invasion. Increased level of miR-214 decreased cell survival and increased cisplatin based cytotoxicity in CC cells. This study showed apoptosis association with increased expression of Caspase 3, 8, 9 and Bax. Overall, findings disclosed the miR-214 a potential target for development of new treatment strategies[79]. Another, miRNA and miR-181a negatively modulate the PKCD expression, through 3 UTR binding hence it results in decreased apoptosis based upon radiotherapy and block G2/M phase[121]. The miR-18a may be applied as biomarker to recognize chemo sensitivity in CC patients to cisplatin treatment. Besides miR-181a role in radio resistance, it reflects chemo resistance in CC. The miR-181a significantly overexpresses in CC patients that do not respond to classical cisplatin treatment. This study also reported upregulation of miR-181a in human CC cell lines to increased chemo resistance using cisplatin through apoptosis reversion[122].

A brief information of miRNA mechanisms allow targeted therapeutic approaches based on either miRNA supplementation or their inhibition[123,124]. As a whole, miRNAs with decrease resistance to radiotherapy or chemotherapy resistance can be achieved by their suppression. Consequently, novel strategy of miRNA inhibition or addition along with radiotherapy or chemotherapy may be established. Such therapeutic approaches using miRNAs with specific expression may be particularly valuable in personalized therapy and target based directed treatment for CC.

CONCLUSION

Alterations in miRNAs expression profile engaged in cell cycle control are mostly events in the development of CC represent a challenging research area. Still information related to miRNAs role in the CC progression and its development is in early stages. More exploration will lead a better understanding towards the functional role of miRNAs and provide new insights into many viral infectious diseases.

SIGNIFICANCE STATEMENT

This study entails the possible role of miRNA in diagnosis, development and progression of cervical carcinoma. This will help the oncologist to better understand the possible role of miRNA in CC diagnosis, their therapeutic applications, treatment outcome along chemotherapy and radiotherapy.

ACKNOWLEDGMENTS

Thanks to Dr. Ayman Khalid Johargy (Medical Microbiology, College of Medicine) for helping us in key understanding and explanation regarding the miRNAs expression profile, dysregulation in CC. The present study was submitted by A.J in partial fulfillment of the professional requirements at Umm Al-Qura University (UQU), Saudi Arabia. The authors are extremely thankful for the support and encouragement to the UQU for providing this opportunity.

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