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A Comprehensive Review of Dysregulated miRNAs Involved in Cervical Cancer

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Abstract: MicroRNAs(miRNAs) have become the center of interest in oncology. In recent years, various studies have demonstrated that miRNAs regulate gene expression by influencing important regulatory genes and thus are responsible for causing cervical cancer. Cervical cancer being the third most diagnosed cancer among the females worldwide, is the fourth leading cause of cancer related mortality. Prophylactic human papillomavirus (HPV) vaccines and new HPV screening tests, combined with traditional Pap test screening have greatly reduced cervical cancer. Yet, thousands of women continue to be diagnosed with and die of this preventable disease annually. This has necessitated the scientists to ponder over ways of evolving new methods and chalk out novel treatment protocols/strategies. As miRNA deregulation plays a key role in malignant transformation of cervical cancer along with its targets that can be exploited for both prognostic and therapeutic strategies, we have collected and reviewed the role of miRNA in cervical cancer. A systematic search was performed using PubMed for articles that report aberrant expression of miRNA in cervical cancer. The present review provides comprehensive information for 246 differentially expressed miRNAs gathered from 51 published articles that have been implicated in cervical cancer progression. Of these, more than 40 miRNAs have been reported in the literature in several instances signifying their role in the regulation of cancer. We also identified 40 experimentally validated targets, studied the cause of miRNAs dysregulation along with its mechanism and role in different stages of cervical cancer. We also identified and analysed miRNA clusters and their expression pattern in cervical cancer. This review is expected to further enhance our understanding in this field and serve as a valuable reference resource.

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1. INTRODUCTION

miRNAs, the short non-coding RNAs (17-22 nucleotides) were first reported in *C.elegans* [1]. They modulate gene expression either by catalyzing mRNA cleavage or by inhibiting mRNA translation and play significant roles in human development [2]. Over the last decade, researchers have established an association of miRNAs aberrant expression in cervical cancer by expression profiling. miRNAs may be oncogenic or tumor suppressors, with oncogenes being up-regulated and the tumor suppressors being down-regulated in cancers [3]. Various mechanisms like amplification, deletion, mutation involving miRNA loci or dysregulation of transcription factors or epigenetic silencing can be responsible for these alterations [4]. Moreover, evidence supports a role for microRNAs at every stage of cervical cancer initiation, progression and development [5]. These abnormally expressed miRNA affect the expression of various oncogenic or tumor suppressor proteins which, in turn, alter the cellular growth, invasion, and metastatic potential of cervical cancer cells.

Cervical cancer, the third most common female cancer is responsible for 9% and 8% of the total new cancer cases and cancer deaths respectively [6]. Of these about 85% are reported from developing countries. With the second highest population in the world, India alone accounts for 27% (77,100) of the total cervical cancer deaths [6]. Cervical cancer either develops from cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL) [7]. Histologically, cervical carcinoma is classified into squamous cell carcinomas (SCCs in 70-80%) and adenocarcinomas (AdCAs in 5-10%) [8]. It is mainly caused due to the infection of Human papillomavirus (HPV). Introduction of prophylactic HPV vaccines and new HPV screening tests, combined with traditional Pap test screening has greatly reduced cervical cancer. Despite these advances, thousands of women continue to suffer and die of this preventable disease each year. Molecular phenotyping of cervical cancer is opening up the potential for molecularly targeted therapies, among which miRNAs are playing an active role in research.

A few reviews that discuss miRNA dysregulation in cervical cancer have been published in the past [9, 10]. Reshmi and Pillai, 2008 briefly covered description about only a few miRNAs and targets. Zheng and Wang, 2011 have also reviewed how HPV proteins deregulate the expression of miRNAs. Following them more studies have been undertaken showing dysregulation of various miRNAs in cervical cancer, especially focussing on target prediction, mechanism of action and their role in each stage of cervical cancer initia-

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tion, progression, and development. Thus, it is very important to summarize the current studies so that researchers and clinicians can acquire an up-to-date understanding of miRNA's role in cervical cancer. This comprehensive review aims to provide information about miRNAs dysregulation in cervical cancer and identify a few that can be useful in the treatment of cervical cancer. In this review we have collected, analysed and discussed the chromosomal location, region, classification (oncogene/tumor suppressor), differential expression, validated targets, cause and working mechanism of miRNAs shown to be dysregulated in different stages of cervical cancer.

2. DIFFERENTIAL CATEGORIZATION

An extensive literature search was performed that identified 51 research articles describing 246 dysregulated miRNAs involved in cervical cancer. There are 41 miRNAs that are reported in 5 or more references while 116 miRNAs have been reported in more than one study (Fig. **1**).

2.1. Chromosomal Location

Earlier studies have shown an association between the genomic position of miRNA and the regions associated with cancer [11]. It was Calin *et al.* in 2002 who first noticed this and reported deletion of miR-15a and miR-16–1 (located at chromosome 13q14) in leukemia [12] followed by reports in solid tumors such as breast cancer [13]. Several other studies also found that miRNA genes are often present at fragile sites, breakpoint region, minimal regions of loss of heterozygosity (LOH) and amplicons [14]. These observations encouraged us to decipher the distribution of dysregulated miRNA on the basis of chromosomal location in cervical cancer (Fig. **2**).

We found that human chromosome 1, 14, 17, 19 and X contain significantly more miRNA genes than others. Previous studies have reported the association of chromosome 1 with malignant transformation in various cancers, including cervical cancer [15, 16]. Various chromosomal abnormalities like aneusomy [17, 18] and LOH in chromosome 1 have been related to cervical cancer [19]. In addition, 5 oncogenes were mapped to this chromosome. Debacker and Kooy identified many new fragile sites in human with the highest number on chromosome 1 [20]. Moreover, gain in chromosomal region of 1 was also observed in multidrug resistant cells [21]. We noted that most of the miRNAs are located on chromosome 1, more specifically 1q24, and are up regulated in cervical cancer, thus serving as oncogenes. In an array of human cancers like breast [22], thyroid [23] and oesophageal cancer [24], chromosome 17p has been reported to be frequently deleted. Also, loss of chromosome 17 [25] or sequence present in its short arm [26] has been frequently observed in cervical carcinogenesis. Our analysis reveals that most of the cervical cancer related miRNAs present in 17q act as oncogenes, similar to observations for chromosome 1 related miRNAs. 19p13.3 has also been documented to be often deleted in cervical adenocarcinoma (CAC), which is a key loci of LOH for CAC [27]. Copy number of 19q13 increases in pancreatic, bladder, colorectal, ovarian and thyroid carcinoma [28]. We observed that most of the miRNAs located on chromosome 19 were present in 19p13 and 19q13 regions. X inactive-specific transcript (XIST) RNA expression is lost in female cancers like breast and cervical cancer cell lines [29-31]. The disturbances in the regulation of the cell cycle seem to be more strongly connected with the LOH in X chromosome [32]. Numerical aberrations of chromosome X were reported in cervical carcinoma [33-35]. X chromosome polysomy was reported in breast tumors as well as chromosomal gain of X is documented to have implications in cell survival [36].

2.2. Chromosomal Region

MiRNAs have been found to be positioned in diverse genomic locations, including 3'UTRs, intergenic, introns, exons and non-protein coding genes [11]. The majority of cervical cancer associated miRNAs lie in the intronic region and very few of them are in 3'UTR (Fig. **3**). Lin *et al.* identified several intron derived miRNAs that were able to induce RNA interference [37]. In another study it was documented that ~40% and 10% of all miRNAs are found within introns of protein-coding genes and long noncoding RNA transcripts respectively [38]. It has been proposed that as intronic miRNAs are processed from the precursor mRNAs, their expression is modulated by the host mRNA expression [39]. However, Monteys *et al.* observed that ~35% of intronic miRNAs have upstream regulatory element for independent expression [40].

2.3. Functional Classification

Depending upon up- or down-regulation of miRNAs, they are termed as oncogenic or tumor-suppressor [41]. Based on this concept we have categorized the putative function of 246 miRNAs and found that the numbers of oncomiRs are high as compared to tumor suppressor (Fig. **4**). We have also observed that a total of 68 miRNAs show variable expressions in different studies functioning either as oncomiRs or tumor suppressors. This may be due to differences in population, conditions and stages of cervical cancer selected for study.

2.4. miRNA Cluster

Several miRNA clusters have been found to be associated with cancer, for example, miR-17/92 cluster is reported as an oncogene in B-cell lymphoma [42]. There are few studies showing the role of miRNA clusters in cervical cancer. Cai *et al.* identified that miR-302-367 cluster blocks cervical cancer cell growth and tumor formation by down-regulating cyclin D1 and AKT1 and up-regulating p27 and p21 proteins [43]. Thus, we searched clusters for 241 miRNAs in miRBase and identified 18 miRNA clusters (Table **1**).

Among these clusters, miR-17-92 cluster has been studied in various cancers like colon cancer [51], breast cancer [52], gastrointestinal cancer [53], lung cancer [54], pancreatic cancer [55]. The miRNAs present in this cluster are located in chromosome 13 and are upregulated in SCC compared to normal. This shows that miR-17-92 cluster acts as oncogene in cervical cancer. Targets for miR-19a, miR-19b and miR-20a have been validated in cervical cancer [50, 56] which promote growth, migration and invasion of cancer cells. In contrast to Li *et al.* [49] and Wilting *et al.* [44], Wei *et al.* [57] showed that miR-17-5p targets TP53INP1 and acts as a tumor suppressor in cervical cancer cells. Thus, the biological mechanism of miRNA cluster in cervical cancer requires further study.

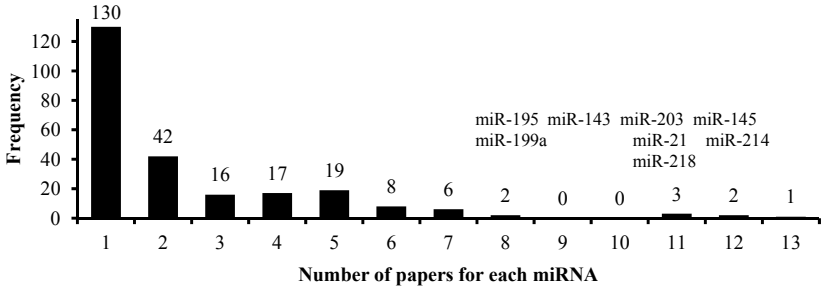


Fig. (1). Number of dysregulated miRNAs repeated in papers.

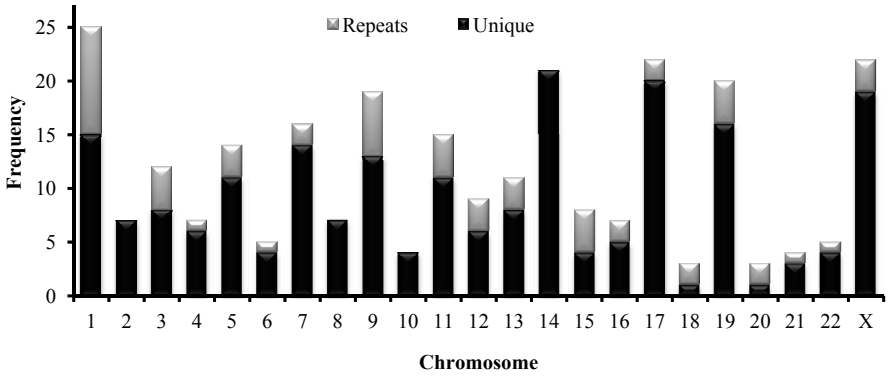


Fig. (2). Location of each dysregulated miRNA in human chromosomes.

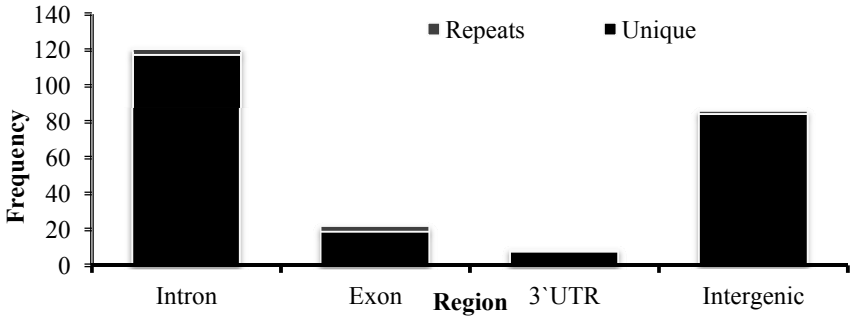


Fig. (3). Region wise distribution of miRNAs.

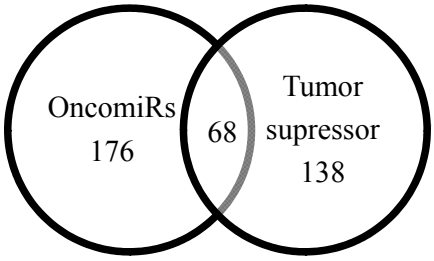


Fig. (4). Shows numbers of oncomiRs, tumor supressors and miRNAs that can function as either an oncomiR or a tumor suppressor.

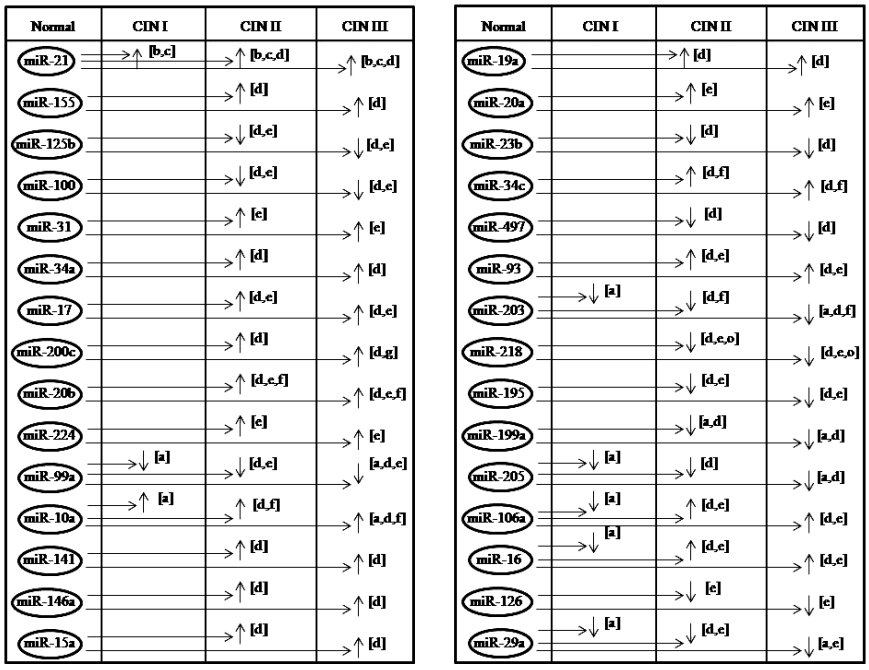
3. EXPRESSION PROFILE ANALYSIS

It is now well known that abnormal expressions of a few miRNAs on several occasions lead to tumor genesis and disease progression. Therefore, miRNA expression profiles are becoming useful to identify novel biomarkers for tumor diagnostic, prognostic and cervical cancer stage characterization [45]. Huang *et al.* demonstrated that low levels of miR-100 and 125b could be indicative of a poor prognosis [58]. A recent study showed that miR-497 may act as a potential prognostic marker and function as tumor suppressor [59]. Thus, to assess variation in miRNA expression in different cervical cancer stages (CIN I, II and III) we analyzed them. However, as different expression patterns have been documented in different studies pertaining to cervical cancer, we considered only those miRNAs that exhibit consistent expression pattern in at least 60% of the studies. (Fig. **5**) shows expression profile for 30 miRNAs in different stages of cervical cancer. Our analysis indicates that 2 of the miRNAs are downregulated (miR-21 and miR-10a) while 4 miRNAs are upregulated during transition from normal to any of the CIN stages (I, II or III). Investigators have also used miRNA expression signatures to define miRNA markers that may provide favorable prognosis. Among these 6 miRNAs, miR-21 and miR-203 are the most studied miRNAs. miR-21 acts as a biomarker for various cancers like ovarian cancer [60], colorectal cancer [61] and esophageal squamous cell carcinoma [62]. There are some miRNAs that show different directions of expression during the transition from low to high grade cervical cancer. miR-106a and miR-16 show decreased

Table 1. miRNA cluster with expression.

miRNA Cluster	Expression (SCC vs Normal)
miR-181d; miR-181c	U[44]; U[45]
miR-191; miR-425	U[44]; U[44, 46]
miR-212; miR-132	D[44]; U[45]
miR-429; miR-200a; miR-200b	U[47]; U[45, 47]; U[47]
let-7e; miR-99b; miR-125a	U[45, 48]; U[46, 47]; U[44]
miR-106b; miR-93; miR-25	U[44]; U[44, 47, 49]; U[44, 45, 49]
miR-141; miR-200c	U[44, 47]; U[44, 47]
miR-497; miR-195	D[44, 47]; D[44, 45, 47, 49]
miR-143; miR-145	D[44, 46, 47]; D[47, 49]
miR-98; let-7f-2	U[45]; U[48]
miR-215; miR-194-1	U[45]; U[45]
miR-29c; miR-29b-2	U[44, 49]; U[44, 45]
miR-30e; miR-30c-1	U[44, 45]; U[44]
let-7d; let-7a-1; let-7f-1	U[44, 45, 48]; U[48]; U[48]
miR-18a; miR-92a-1; miR-17; miR-19a; miR-19b-1; miR-20a	U[44, 47]; U[44, 49]; U[44, 49]; U[44, 45, 50]; U[44, 50]; U[47, 49]
miR-15b; miR-16-2	U[44, 45, 49]; U[44, 45, 49]
miR-15a; miR-16-1	U[44, 45, 49]; U[44, 45, 49]
miR-100; let-7a-2	D[44, 47, 49]; U[48]

Legend: U and D refer to Upregulated and Downregulated respectively.



Legend:
a: [64]; b: [65]; c: [66]; d: [44]; e: [49]; f: [67]; g: [47]; h: [45]; i: [46]; j: [48]; k: [58]; l: [50]; m: [68]; n: [69]; o: [70].

Fig. (5). Expression profile analysis of miRNAs dysregulated in cervical cancer.

expression in CIN I but increased expression in CIN II-III. The increased expression of these miRNAs may contribute to transition from low grade to high grade cancer. Also, these miRNAs can be used to discriminate between CIN stages. However, more such studies focussing on the expression of these miRNAs need to be undertaken. In the last few years, the detection of circulating miRNAs in the body fluids using microarray and quantitative PCR has enabled their use as diagnostic biomarkers. For example: miR-20a, a circulating miRNA was shown to act as a potential biomarker for detecting the lymph node status of cervical cancer patients [63].

4. CAUSES OF DISTURBED miRNA EXPRESSION IN CERVICAL CANCER

Several mechanisms can control miRNA expression and the disturbance therein results in disease initiation including cancer. It is the amalgamation of chromosomal defects like deletions, amplifications or mutations and other genetic/epigenetic events which lead to the down/up regulation of miRNAs (Fig. **6**). The significance of these genomic aberrations in tumorigenesis lies in the fact that these involve the genomic loci where miRNA resides in the primary tumors. Here, we summarize these mechanisms in cervical cancer.

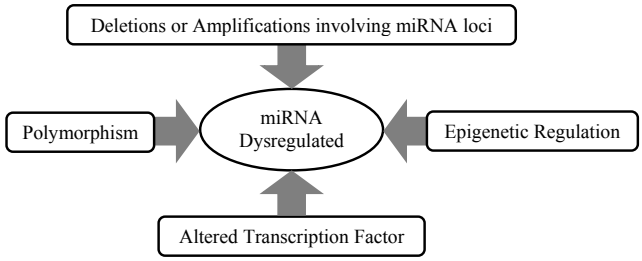


Fig. (6). Depicts different causes of miRNA dysregulation.

4.1. Alteration of miRNA Expression Due to Deletions or Amplifications

As stated earlier, the miRNA genes are commonly present at breakpoint regions, minimal regions of LOH and amplicons as well as at other fragile sites [12]. So, chromosomal alterations are considered as a key primary means responsible for abnormal miRNA expression in cancer. In fact, the relation between chromosomal alterations and differential miRNA expression has been well documented for various cancers [11, 71-73]. The first miRNAs reported to be linked to chromosomal aberration were miR-15a and 16-1. These miRNAs are located on Chromosome 13 which is commonly deleted in Chronic Lymphocytic Leukemia [12]. This evidence supports the fact that miRNAs are often present in genomic regions that are altered in cancer, as indicated by a number of other studies too [11, 14, 74]. LOH is a common and an early event in the development of various cancers including cervical cancer. In cervical cancer, miR-100 (located at chromosome 11q24.1) has been found to be down regulated [47] and the fact that 11q23.3 – 11q24.1 region is related with LOH in cervical cancer has been reported by Zhang *et al.* [75]. Hence, it is possible that LOH may be responsible for the down regulation of miR-100 in cervical cancer. Some of the other general mechanisms of gene activation in tumorigenesis are chromosomal gain and amplification. For example: miR-944, a miRNA that has been shown to be cervical tissue specific, is located at chromosome 3q27-28, a region commonly amplified in cervical cancer [46, 76]. Also, Wilting *et al.* found that aberrant expression of five miRNAs i.e. miR-9 (1q23.2), miR-15b (3q25.32), miR-28-5p (3q27.3), miR-100 and miR-125b (11q24.1), was related to chromosomal alterations [46]. They further analyzed miR-9 and found chromosomal gain of 1q is responsible for its increased expression. Many studies have also shown the association of chromosomal aberration with elevated expression of Drosha which influences global miRNA profiles in cervical cancer. Some of the other studies demonstrated that in cervical cancer, gain of chromosome 5p is connected with over-expression of miRNA-processing enzyme Drosha and altered miRNA expression profiles [77-79]. This drosha overexpression is suggested to be a vital mechanism for cervical cancer progression in the later stages as it leads to elevated level of mature miRNAs which in turn affects transcription of several mRNAs and the production of other pri-miRNAs [80]. Thus, it needs to be validated whether targeting the miRNA machinery has any role in cancer prevention.

4.2. Epigenetic Regulation of microRNAs in Cervical Cancer

DNA methylation is an epigenetic modification which inhibits gene expressions and thereby alters the phenotype. The involvement of epigenetic alterations in cervical oncogenesis was confirmed in a recent study. Highly significant differences were reported in miRNA hypermethylation between the tumor and control samples [81]. Methylation of miR-124a showed a strong association with high-risk HPV genotype, whereas miR-203 displayed borderline association with high-risk HPV genotype [81]. Wilting *et al.* also established the role of methylation mediated silencing of miR-124 in cervical cancer by treating cell lines with demethylating agent which resulted in the reduction of *miR-124* methylation levels [82]. Further, they established that *miR-124* ectopic expression decreases proliferation by inducing apoptosis. It was also revealed that methylation of miR-149, -203 and -375 increases in different stages of HPV induced transformation with progression to malignancy [83]. Yao *et al.* found that hypermethylation of various miRNA like miR-432, miR-1286, miR-641, miR-1290, miR-1287 and miR-95 is related to HPV infection in cervical cell lines [84]. These observations highlight the significance of aberrant DNA hypermethylation in regulating the expression of miRNA in cervix cancer.

4.3. Polymorphisms in microRNAs or microRNA Binding Sites

Several studies in the recent years have shown that single nucleotide polymorphisms (SNPs) located in the protein [85] or miRNA genes or in binding sites of their target genes modify miRNA expression and/or maturation and are related to the growth of cancer [86]. Studies have also evaluated the link of SNPs in microRNAs and microRNA binding sites to cervical cancer incidence. For example, a study established

that variation in *pri-miR-218* (rs11134527) resulted in changes in *miR-218* expression which influenced the miRNA binding process and hence led to increased cervical cancer susceptibility [87]. Another study showed that polymorphism in hsa-miR-499 (rs3746444 A/G) and hsa-miR-146a (rs2910164 G/C) are linked with cervical SCC [88]. The same miRNA-146a polymorphism (rs2910164) in Chinese population was shown to affect genetic susceptibility to cervical cancer by elevating the expression of mature miR-146a [89]. Various studies provide support to the fact that SNPs in miRNA-binding sites also modulate risk of cervical cancer. For example, a C to T polymorphism in miRNA target site of BCL2 has been demonstrated to be associated with cervical carcinogenesis [90]. Polymorphism in pri-miR-218 (rs 11134527, A/G) and LAMB3 (rs2566, C/T) was responsible for decreasing/increasing cervical cancer pathogenesis respectively [91]. This shows potential for SNPs in microRNA binding sites to modify one's risk of cervical cancer. These studies are population based, which need validation in additional populations and the biological mechanism underlying these associations must be investigated. We believe that future work should be planned to determine if there are other SNPs in miRNA related genes that are associated with prognosis so that clinically useful data can be generated.

4.4. Transcription Factor Regulation of miRNA

Gene expression is known to be regulated by contact between transcription factors (TFs) and upstream regulatory elements of target genes [92]. Furthermore, miRNAs expression can be activated or repressed by TFs, which therefore can serve as miRNA regulators [93]. Thus alteration in miRNA expression could result from variation in transcriptional activity. For, example, a cluster of 6 miRNAs on chromosome 13 is regulated by c-Myc [94]. miR-17-5p and miR-20a which are part of this cluster are dysregulated in cervical cancer [95]. Regulation of miRNAs via TF has been studied only in a few studies and therefore it would be interesting if important miRNAs and regulatory modules in cervical cancer are identified.

5. EXPERIMENTALLY VALIDATED TARGETS

An miRNA targets several hundred genes [96]. Identifying miRNAs, their targets and functions has been an important approach for understanding normal biological processes and their contribution in disease development [97]. The accurate prediction and validation of microRNA targets are essential to understand the function of microRNAs. So far, few targets have been validated for miRNAs dysregulated in cervical cancer (Table **1**). We observed that as compared to other miRNAs (listed in Table **2**) the maximum number of targets (5) have been validated for miR-214. These 5 targets are associated with apoptosis, cell cycle regulation, migration and cell invasion. The other miRNAs that have 3 validated targets are miR-205, miR-34a and miR-133b among which the first two were found to be involved in apoptosis and migration. Also miR-214 and miR-218 are involved in chemotherapy sensitivity/resistivity. Thus, these miRNAs can play an important role in therapeutic treatment of cervical cancer.

Table 2. Experimentally validated targets of dyregulated miRNAs in cervical cancer.

miRNAs	Targets
miR-218	LAMB3[68-70]
miR-143	Bcl-2[98]
miR-21	PDCD4[65, 99]; CCL20[66]
miR-214	MEK3[100, 101]; JNK1[100, 101]; plexin-B1[101]; GALNT7[102]; Bcl2l2[103]
miR-34a	Notch1[104]; Jagged1[104]; p18Ink4c[105]
miR-205	lipid phosphatase SHIP2[46]; CYR61[106]; CTGF[106]
miR-100	Polo-like kinase1 (PLK1)[107]
miR-29a	YY1[49]; CDK6[49]
miR-23b	Urokinase-type plasminogen activator (uPA)[108]
miR-10a	HOX[64]; CHL1[109]
miR-196a	HOX[64]
miR-375	SP1[110]
miR-886-5p	Bax protein[111]
miR-372	CDK2[112]; cyclin A1[112]
miR-133b	MST2[113]; CDC42[113]; RHOA[113]
miR-20a	TNKS2[56]
miR-424	Chk1[114]
miR-19a	CUL5[50]
miR-19b	CUL5[50]
miR-223	FOXO1[115]
miR-17	TP53INP1[57]
miR-125b	PIK3CD[116]
miR-302-367 cluster	cyclin D1[43]
miR-155	SMAD2[117]; CCND1[117]
miR-182	FOXO1[118]
miR-497	IGF-1R[59]
miR-145	IRS-1[119]

6. miRNAs AS BIOMARKERS FOR CHEMORESISTANCE OR CHEMOSENSITIVITY

Chemotherapy is an established and important treatment strategy for cervical cancer. It has been shown that aberrant miRNA expression affects the target proteins and fundamentally silences the target gene [120]. Various investigations support the hypothesis that the over- or under-expression of some miRNAs is directly linked to a patient's response to chemotherapeutic agents. Specific examples of miRNAs

related to chemoresistance have been discussed in the literature. For example, it has been reported that the sensitivity to mitomycin was increased and the chemoresistance induced by glucocorticoids was reversed by the over-expression of miR-145 in cervical cancer cells [119]. Cisplatin, a broad-spectrum anticancer agent, is used in curing several cancers, including cervical cancer [121]. However, many cervical cancer patients show resistance to its chemotherapy [122]. Various studies have now shown that ectopic expression of miRNAs like miR-15b, miR-16 [123], miR-218 [124], miR-155 [117] and miR-214 [103] enhances sensitivity to cisplatin. It has also been documented that the Bcl-2 expression level is linked with response to cisplatin [125]. miR-15b, miR-16 and miR-214 are the three miRNAs which target Bcl-2 and enhance sensitivity to cisplatin-based combination chemotherapy. Additionally, miR-218 has been shown to increase cisplatin chemosensitivity by inhibiting Rictor protein, which is part of AKT-mTOR pathway. The above studies clearly demonstrate the role of miRNAs in chemosensitivity/resistance, and show that manipulating miRNAs may be beneficial in modulating cervical cancer treatment. Thus, the therapeutic development of miRNA mimics or antagomirs may reveal novel therapies and improve prognosis for cervical cancer.

7. ROLE OF miRNA IN DIFFERENT STAGES OF CERVICAL CANCER

Various researchers have shown the implications of miRNA on various biological processes, including apoptosis, cell cycle, invasion and migration, which are responsible for the development of cervical cancer. Based on observations obtained from these studies we have summarized biological pathway specific miRNA functions (Table **3**) in cervical cancer.

7.1. miRNAs in Cervical Cancer Progression

Cancer stem cells regulate tumor growth by propagating differentiated cancer cells [127], which lose control of the normal cell cycle during cancer progression. Here, we will highlight those miRNAs that have been identified as apoptosis and cell cycle regulators of cervical cancer development.

7.1.1. Apoptosis

Apoptosis has an important role in the normal process and functioning of cervical tissue. Involvement of miRNAs in cell death regulation was first reported in 2003 when the miR-14 was shown to regulate apoptosis in Drosophila [128]. Apoptosis is regulated by various proteins (Fig. **7**). Bcl-2 family, which is comprised of many proteins, is a nodal factor of the apoptotic pathway and is classified into three functional groups. The group I members include Bcl-2 and Bcl-xL, possess anti-apoptotic activity; group II comprises of Bax and Bak, have pro-apoptotic activity and group III members, such as Bim and Bad, also possess pro-apoptotic activity [129]. Liu *et al.* showed that miR-143 over-expression promoted apoptosis and inhibited HeLa cell growth while anti-miR143 rescued the effects [98]. Furthermore, miR-143 suppressed the luciferase reporter activity carrying 3'-UTR of Bcl-2, which was abolished upon mutating miR-143-binding site, demonstrating that Bcl-2 is a miR-143 target gene. This investigation revealed that miR-143 by indirectly targeting Bcl-2 operated as an anti-apoptotic factor. In contrast, miR-886-5p was found to be upregulated in cervical cancer and targets Bax protein. At the time of apoptosis, Bax and/or Bak protein damage the outer mitochondrial membrane which leads to the release of cytochrome c and activates caspase and caspase-9, that leads to the eventual cell death [130].

For a cell to survive it is necessary that the apoptosis process remains halted, a task that is accomplished by inhibiting pro-apoptotic factors. Although there are various pathways which lead to inhibition of pro-apoptotic proteins, the best characterized one in cervical cancer is the Akt signaling pathway. It has been reported that tumor suppressive miR-218 reduced cervical cancer growth by inhibiting AKT-mTOR signaling pathway. Also, miR-218 overexpression has been documented to diminish both Rictor and Phospho-AKT level in HeLa cells [124]. So our hypothesis is that miR-218 targets the mTOR component Rictor which in turn blocks phosphorylation of AKT in cervical cancer, similar to what is demonstrated in oral cancer [131]. Similarly, another protein, SHIP2 (SH-2 containing inositol 5'-phosphatase 2) which is a ubiquitous lipid phosphatase, is target of miR-205 [46]. SHIP2 is known to dephosphorylate the vital secondary messenger phosphatidyinositol 3,4,5-triphosphate (PIP3) that regulates several key cell signaling pathways, including Akt and thus enhances apoptosis and cell death [126]. It has also been shown that inhibition of miR-205 activity in aggressive squamous cell carcinoma decreases the level of phosphorylated Akt and BAD proteins and thus enhances the apoptosis rate [126].

Table 3. miRNAs in different biological processes in cervical cancer.

Apoptosis	Cell Cycle	Metastasis
miR-143 (chr 5)[98]	miR-223 (chr X)[115]	miR-205 (chr 1)[106]
miR- 214 (chr 1)[100]	miR-424 (chr X)[114]	miR-155 (chr 21)[117]
miR-218 (chr 4; 5)[124]	miR-302-367 (chr 4)[43]	miR-214 (chr 1)[101, 102]
miR-205 (chr1)[126]	miR-29 (chr 7)[49]	miR-218 (chr 4; 5)[69]
miR-886-5p[111]	miR-214 (chr 1)[100]	miR-21 (chr 17)[65]
	miR-100 (chr 11)[107]	miR-23b (chr 9)[108]
	miR-372 (chr 19)[112]	miR-375 (chr 2)[110]

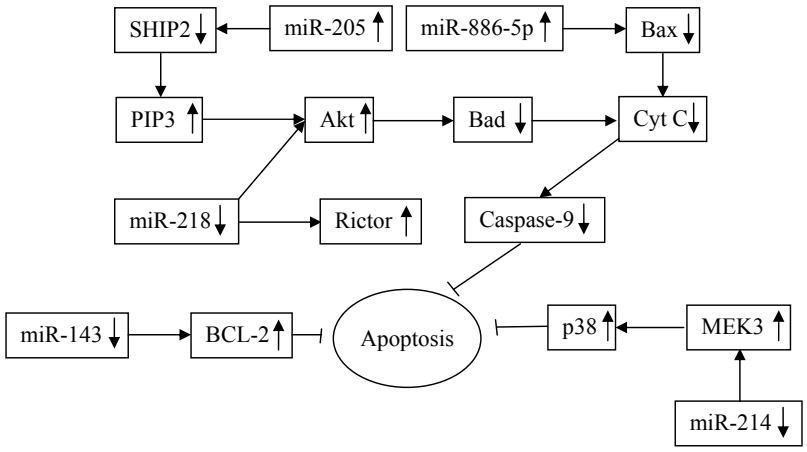


Fig. (7). Network for miRNAs and their targets involved in apoptosis in cervical cancer.

Legend:

↑ represents upregulation, ↓ represents downregulation, ⊣ represents inhibition.

A member of the MAPK family participating in apoptosis is MEK3/p38 pathway. Yang *et al.* showed that MEK3 is the direct target of miR-214 [100]. Over expression of MEK3 results in upregulation of p38, which is for the induction of apoptosis [132]. The mechanism of this remains unclear in cervical cancer. Clearly, the events unfolding miRNA-mediated apoptosis in cervical cancer are not well understood and therefore require further investigation.

7.1.2. Cell Cycle Dysregulation

The normal cells are controlled by cell cycle proteins, whose dysregulation results in uncontrolled growth leading to cancer progression [133]. In recent times, various miRNAs have been studied to show role in altering cell cycle by modulating the regulators involved in the pathway. In the next paragraphs we discuss miRNAs role in cell cycle regulation within cervical cancer (Fig. **8**).

The cyclin dependent kinase pathway is a vital regulator of the cell cycle, which is shown to be modulated by several miRNAs in cervical cancer. For example, miR-29a is negatively correlated with CDK6 [49]. CDK6 is active during G1 and its activity relies on cyclin D1. Cyclin D1 levels rise just before the transition from G1 to S. Due to the high expression of cyclin D1 and CDK6 transcripts caused by low miR-29 expression there are a lot of cyclin D1/CDK6 complexes. These events result in uninhibited phosphorylation of Rb and thereby cell proliferation that leads to the development of cancer [134]. Cyclin D1 is indirectly targeted by miR-214. Yang *et al.* showed that in cervical cancer miR-214 is down regulated and targets 3'UTR of c-Jun NH_2-terminal kinase1 (JNK1) [100]. JNK1 targets the members of activating protein1 (AP1) TF group, which then controls various processes including proliferation. Activated JNK1 induces cMyc, which suppresses p21 expression and promotes cell proliferation through cyclin D1 expression. JNK1 also upregulates c-Jun which suppresses p53 [135]. Similarly, CDK2 and cyclin A1 are targeted by miR-372 and controls cell cycle [112]. Cyclin A1 first along with Cdk2, activates DNA replication and then with Cdk1 drives mitosis [136].

p53 a tumor suppressor protein, plays an important role in preventing uncontrolled cell division [137, 138]. Yin Yang 1 (YY1), a transcription factor belonging to the zinc finger class, is found to be a potential target of miR-29a [49]. YY1 is known to be implicated in the regulation of cell growth, development, and differentiation [139]. YY1, MDM-2 and p53 are known to form a ternary complex, which is necessary for MDM-2 to ubiquinate p53 [139]. This event results in the p53 translocation to the proteasome and subsequently its degradation. Therefore, it is observed that YY1 overexpression reduces endogenous p53 level. As YY1 is also As_2O_3 target, it could act as a potential drug target for anti-cervical cancer therapy [140].

In cancerous cells, checkpoints are frequently bypassed by overexpression of mitotic kinases that control them. PLK1 is an important checkpoint protein involved in G2/M phase transition, which is targeted by miR-100 in cervical cancer [107]. Overexpression of PLK1 results in cyclin B1 and Cdc25C hyperactivation, which triggers entry into mitotic phase of cell cycle [141]. Xu *et al.* showed that expression levels of checkpoint kinase 1 (Chk1) and p-Chk1 are inversely correlated with miR-424 in cervical cancer. They also demonstrated that over expression of miR-424 inhibited Chk1 while RNAi-mediated knockdown of Chk1 decreased matrix metalloproteinase 9 expression [114].

Forkhead box protein O1 (FOXO1) is a key constituent of the forkhead transcription factor family. The unphosphorylated active form of FOXO1 increased in the cells, which correlated with downregulation of the CDK inhibitors $p27^{Kip1}$ and $p21^{Cip1}$ and upregulation of cyclin D1 at either mRNA or protein level [115]. It was found that miR-223 [115] and miR-182 [118] directly target FOXO1 and are downregulated in cervical cancer cells. Similarly, it was demonstrated that miR-302-367 cluster downregulates cyclin D1 and AKT1 and upregulates p27 (Kip1) and p21 (Cip1), leading to the inhibition of cervical cancer cell growth [43]. Thus, it is interesting to speculate the contribution of dysregulated miRNAs to cervical cancer progression through deregulation of cell cycle regulatory pathway.

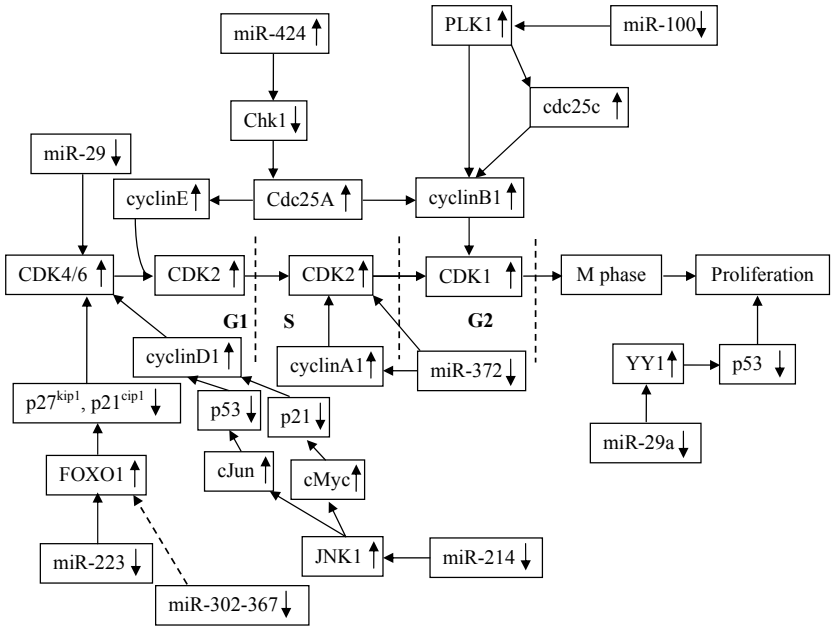


Fig. (8). Cell cycle regulation by miRNA and their targets dysregulated in cervical cancer.

Legend:

↑ represents upregulation, ↓ represents downregulation, - - → represents unknown pathway.

7.2. miRNAs in Cervical Cancer Metastasis

Subsequent to initiation and progression, cancer cells proceed towards invasion and metastasis. This process is started by piercing through the epithelial basement membrane, a development characterized by epithelial-mesenchymal transition (EMT). Several regulators including miRNAs have been shown to modulate this process in cervical cancer (Fig. **9**). For instance, *miR-205* represses cell migration/invasion through EMT in cervical cancer tissue [106]. They found that miR-205 targets CYR61 and CTGF proteins, which play varied role in cellular processes like cell proliferation, adhesion, migration, angiogenesis and tumorigenesis [142] through interaction with cell surface receptors like integrin receptors and heparansulfate proteoglycans. Similarly, miR-155 down expression is shown to be associated with migration/invasion of cervical cancer. Lei *et al.* suggested that miR-155 inhibits SMAD2 expression and thus regulates EMT negatively [117]. They also showed that miR-155 overexpression resulted in upregulation of TP53 activity and thus reversed EMT.

During invasion, metalloproteinases (MMP) play an essential role by degrading the extracellular matrix, which is the extracellular part of the tissue and mediates cell attachment [143]. Urokinase-type plasminogen activator (uPA), a serine protease initiates the activation of metalloproteinases as well as the conversion of plasminogen to plasmin, thus conferring cancer cells with the capability to degrade surrounding extracellular proteins [144]. uPA is among the biomarkers that have high expression in cervical tissues and thus could be useful to diagnose cervical carcinoma [145]. Oncogenic HPV-16 E6 protein downregulates miR-23b, which in turn increases the expression of uPA to induce migration in human cervical cancer cells [108]. Recent reports suggest that uPA is one of the gene targets for miR-23b in hepatocellular carcinoma cells [146]. The active PAI-1, a serine protease inhibitor (serpin) reduces invasive phenotype in ovarian and breast cancer cell lines, thus signifying the role of uPA [147]. Also, it has been revealed that miR-21 inhibits PDCD4 which thereby affects invasion and metastasis [65]. Though, the mechanism by which PDCD4 regulates cell invasion process is unclear, it has been suggested to act through binding to the eukaryotic translation initiation factor 4A (eIF4A), which then regulate AP-1 and subsequently the MMP [148, 149].

In another study, it was demonstrated that in cervical cancer miR-214 was down-regulated while its expression reduced the growth of cervical cells. They also showed that miR-214 targets UDP-*N*-acetyl-α-D-galactosamine:polypeptide *N*-acetylgalactosaminyltransferase 7 (GALNT7) and inhibits its expression [102]. GALNT7 functions as a follow-up enzyme in the initiation step of O-glycosylation. Many studies have shown that aberrant glycosylation is a major event for oncogenic transformation as well as invasion and metastasis [150]. Also, Qiang *et al.* showed that in cervical cancer miR-214 is downregulated and targets plexin-B1 [101]. Moreover, repression of plexin-B1 leads to proliferation, migration and invasion of HeLa cells. Further, plexin-B1 binds to Sema4D/CD100 [151], which results in recruitment and sequestration of active Rac. This prevents Rac to activate PAK leading to the disassembly of cytoskeletal structures [152]. Recently it was also found that activation of plexin-B1 by Sema4D activates RhoA leading to endothelial cell migration [153].

Yamamoto *et al.* have shown that downregulation of miR-218 results in increased expression of LAMB3 contributing to cancer cell migration and invasion in cervical SCC [69]. Laminin-332, a heterotrimer composed of 3 chains (LAMA3, LAMB3 and LAMC2), regulates cell migration

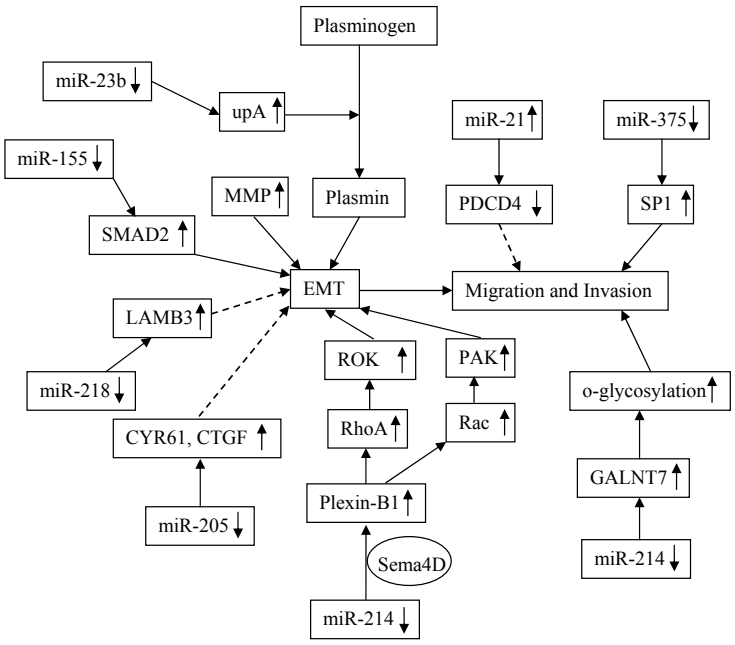


Fig. (9). Network for miRNAs involved in migration and invasion of cervical cancer cells.

Legend:

represents upregulation, represents downregulation, represents unknown pathway.

[69]. Laminin-332, a heterotrimer composed of 3 chains (LAMA3, LAMB3 and LAMC2), regulates cell migration during regeneration and repair processes [154, 155]. Laminin-332 is shown as an invasiveness marker in cervical lesions [156] and binds to several cell-surface receptors [157-159]. Among these binding partners, integrins are cell surface transmembrane proteins that mediate extracellular signals and intracellular pathways, leading to the control of the cell cycle, cell migration, and invasion of cancer cells [160]. But, they have not analyzed the signal pathways associated with the interactions of integrins and laminin-332 in cervical SCC.

Angiogenesis, an essential process during metastasis, is driven by overexpression of various angiogenic factors like vascular endothelial growth factor (VEGF) [161]. Sp1 is a link between the mitogen-activated protein kinase (MAPK) pathway and vascular endothelial growth factor (VEGF) expression [162]. Wang *et al.* demonstrated that miR-375 targets the 3'UTR of SP1 and knockdown of SP1 reduces cell migration and invasion [110]. Moreover, elevated miR-375 suppresses cell proliferation by blocking G1-to-S transition in cervical cancer. VEGF is a potent inducer of angiogenesis and various studies have shown VEGF as a direct target of miRNAs associated with many cancers [163]. Therefore, miRNAs that are either targeting or participating VEGF-mediated angiogenesis should be elucidated in cervical cancer.

8. CONCLUSION

Accumulating evidence suggests that miRNAs have emerged as an important player in carcinogenesis. In the present comprehensive review, we collected 246 dysregulated miRNAs and 40 validated targets in cervical cancer through literature search. We analyzed miRNAs on the basis of chromosomal location, region, functional classification, studied the cause of miRNA's dysregulation, probable mechanisms, roles in different stages of cervical cancer as well as identified miRNA clusters. The analysis shows that miRNAs affect various biological pathways in cervical cancer and thus can be developed for cervical cancer detection and therapy. More studies need to be performed to further elucidate therapeutically important miRNAs for cervical cancer treatment.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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