



The Role of microRNAs, Long Non-coding RNAs, and Circular RNAs in Cervical Cancer

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Prolonged infection of uterine cervix epithelium with human papillomavirus (HPV) and constitutive expression of viral oncogenes have been recognized as the main cause of the complex molecular changes leading to transformation of cervical epithelial cells. Deregulated expression of microRNAs (miRNA), long non-coding RNAs (lncRNA), and circular RNAs (circRNA) is involved in the initiation and promotion processes of cervical cancer development. Expression profiling of small RNAs in cervical neoplasia revealed up-regulated “oncogenic” miRNAs, such as miR-10a, miR-21, miR-19, and miR-146a, and down regulated “tumor suppressive” miRNAs, including miR-29a, miR-372, miR-214, and miR-218, associated with cell growth, malignant transformation, cell migration, and invasion. Also several lncRNAs, comprising among others HOTAIR, MALAT1, GAS5, and MEG3, have shown to be associated with various pathogenic processes such as tumor progression, invasion as well as therapeutic resistance and emerged as new diagnostic and prognostic biomarkers in cervical cancer. Moreover, human genes encoded circular RNAs, such as has_circ-0018289, have shown to sponge specific miRNAs and to concur to the deregulation of target genes. Viral encoded circE7 has also demonstrated to overexpress E7 oncoprotein thus contributing to cell transformation. In this review, we summarize current literature on the complex interplay between miRNAs, lncRNAs, and circRNAs and their role in cervical neoplasia.

Keywords: cervical cancer, long non-coding RNA, circular RNA, microRNA, human papillomavirus (HPV)

INTRODUCTION

Cervical cancer is the fourth most frequently diagnosed tumor and the fourth leading cause of cancer death in women in the world with ~570,000 cases and 311,000 deaths in 2018 (1). The persistent infection with carcinogenic human papillomaviruses (HPV) has shown to be the necessary cause of ~95% of invasive cervical cancer, including cervical squamous cell carcinoma (SCC) and adenocarcinoma (AC) histotypes (2). Cervical SCC is generally preceded by persistent squamous intraepithelial lesions (SIL) caused by HPV infection, therefore the detection of viral nucleic acids has shown to be valuable for the effective prevention of cervical cancer development in oncologic screening programs (3).

The E6 and E7 oncoproteins encoded by high risk HPVs are considered the main players of the multistep transformation process affecting the infected cervical cells. Indeed, they are able to inhibit p53 and pRb oncosuppressors, respectively, and to interact with a plethora of cell signaling factors regulating cell cycle, genome stability and epigenetic modifications (4, 5). Moreover, the HPV E5 protein has also a relevant role in tumor cell invasion and metastasis for its ability to increase the expression of the epidermal growth factor receptor (EGFR) and c-MET, the latter being also critical for viral gene expression (6, 7).

Nevertheless, the gradually accumulation of genetic and epigenetic alterations in HPV infected cells is also crucial for the ultimate progression to cervical cancer. The mutational profile of cervical carcinoma showed the presence of non-synonymous somatic nucleotide changes in PIK3CA, PTEN, TP53, STK11, and KRAS genes (8–11). Recent advances in cancer genome sequencing allowed to identify further unknown mutations in MAPK1, HLA, EP300, FBXW7, NFE2L2, ERBB3, CASP8, TGFBR2, and SHKBP1 genes as well as sequence amplifications in CD274 (PD-L1), PDCD1LG2 (PD-L2), and BCAR4 (lncRNA BCAR4) genes (12, 13). In addition, activating mutations creating *de novo* transcription factor binding sites in regulatory regions, such as the TERT promoter sequence, have been identified in a significant fraction of cervical SCC (14).

Epigenetic modifications, including deregulation of microRNA (miRNA), long non-protein coding RNA (lncRNA) and circular RNA (circRNA) levels, have shown to play important roles in cell transformation during distinct stages of cervical intraepithelial neoplasia and cervical carcinoma development [Figure 1; (15–17)].

MiRNAs are small (19–25 nucleotides long), single-stranded non-coding RNAs that regulate gene expression mainly by binding to sequence motifs located within the 3' untranslated region (UTR) of mRNA transcripts (18, 19). Other regulatory functions include their reciprocal interaction on primary miRNA transcription processes, binding to double-stranded DNA to form triple helixes as well as interaction with RNA G-quadruplex structures that interfere at specific gene regulatory sites (20). The differential expression of the ~2,500 miRNAs encoded by the human genome has an important role in the embryo development and in the physiological functioning of tissues and organs (21, 22). Several miRNAs have oncogenic or tumor suppressor activities and play a fundamental role in cancer development, progression and dissemination (23). A recent meta-analysis of miRNA profiles in cervical neoplasia cases and normal cervical epithelium samples identified 42 up regulated and 21 down regulated miRNAs among different stages of cervical neoplasia (24). The pathway enrichment analysis of genes targeted by these miRNAs revealed the alteration of p53, ErbB, MAPK, mTOR, Notch, TGF β , and Wnt pathways all contributing to hallmarks of cancer (24).

lncRNAs are regulatory transcripts longer than 200 nucleotides mostly transcribed by RNA pol II and characterized by a 5' 7-methylguanosine cap and a 3' poly (A) tail similarly to messenger RNAs (25). Despite being not translated into full-length proteins, lncRNAs are implicated in a variety of biological

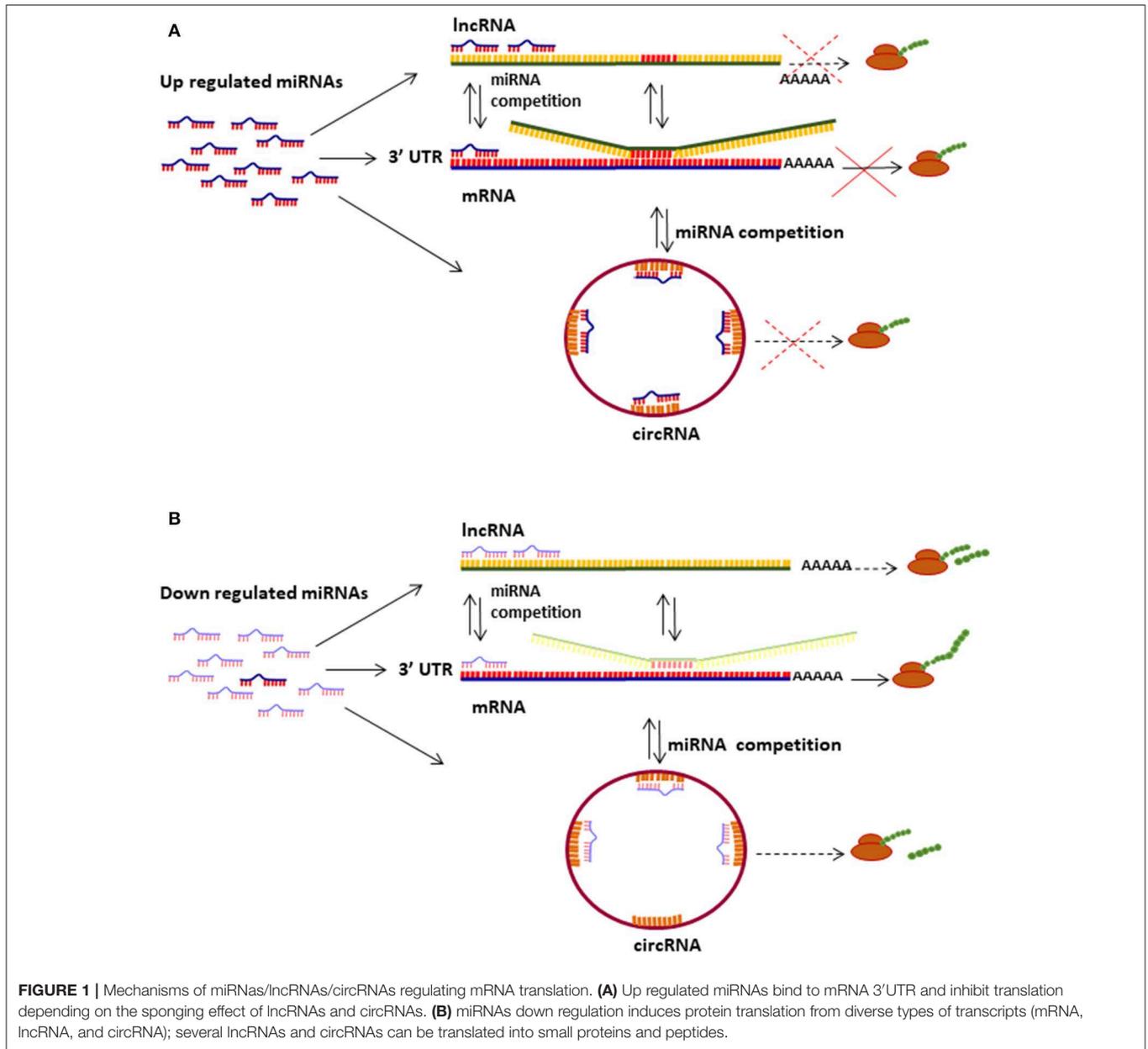
activities such as regulation of gene transcription mediated by their interaction with chromatin-modifying complexes at specific regulatory regions, decoy for transcription factors and miRNAs as well as scaffolding for functional ribonucleoprotein complexes organization (26, 27). Deregulation of lncRNAs expression is associated with cardiovascular and neurodegenerative diseases as well as with cancer development (27, 28). Around 14 lncRNAs have shown to be altered in cervical carcinoma affecting important metabolic pathways such as STAT3, wnt/ β -catenin, PI3K/AKT, and Notch signaling (29). Moreover, some lncRNAs, including MALAT1, CCEPR, and TMPOP2, are reciprocally regulated by HPV16 E6 and E7 expression hence enhancing the oncogenic effect of viral oncoproteins in the progression of cervical neoplasia (30, 31).

The single-stranded closed RNA molecules (circRNA) are a new class of non-coding RNAs, originating from back-splicing of pre-mRNAs, that have several biological functions in normal cells including the ability to act as sponges to efficiently subtract microRNAs and proteins (32). CircRNAs have shown to be aberrantly expressed in a tissue-specific manner in cancer cells and to contribute to cancer development by perturbing cell proliferation, migration, and angiogenesis processes (33). Several studies indicated that circRNAs play a significant role in cervical cancer development by different molecular mechanisms, which among them miRNA sponging is the most important (34). A recent study investigating circRNA expression in cervical cancer tissues by microarray analysis showed that 45 circRNAs were upregulated and that the most expressed has_circ_0018289 was involved in the direct binding of miR-497 (35).

The aim of this review is to summarize the recent studies on the role of miRNAs, lncRNAs, and circRNAs as well as their reciprocal regulation in different stages of cervical neoplasia. Moreover, it provides an overview of the potential impact of non-coding RNAs in the diagnosis and therapy of cervical cancer.

THE ROLE OF miRNAs IN CERVICAL NEOPLASIA

Many studies have evaluated the expression levels of miRNAs in cervical neoplasia biopsies as well as in exfoliated cervical cells, in cervical mucus and in the serum of women diagnosed with cervical cancer (Table 1). The first study describing the differential expression of six miRNAs (let-7b, let-7c, miR-21, miR-23b, miR-196b, and miR-143) in human cervical carcinoma cell lines in comparison with normal cervical samples was published by Lui et al. (107). Numerous investigations since then have been conducted in order to characterize the mechanisms causing miRNAs deregulation as well as their expression pattern in cervical cancer tissues vs. normal cervical epithelia. Indeed, genetic alterations of miRNA loci such as gene deletions, amplifications, or mutations as well as epigenetic silencing such as DNA methylation or deregulation of miRNA processors and transcription factors have been all associated with aberrant expression of miRNAs in cervical cancer (108). For example, Wilting et al. identified 89 deregulated miRNAs in cervical SCC with miR-9 over expression significantly



associated with chromosome 1q gain and with increased cell viability, anchorage-independent growth and cell migration (36). Moreover, Muralidhar et al. identified 16 deregulated miRNAs, including miR-21, miR-29a, miR-31, and miR-203, in advanced cervical SCC which were associated with the up regulation of miRNA processor Droscha transcript and gain of chromosome 5p (109).

Numerous studies over the past decade have analyzed the miRNAs expression to identify significant variations during the transition from low to high grade cervical neoplasia and to invasive cervical cancer in order to define novel biomarkers for cervical cancer diagnosis, prognosis and cancer stage (24, 37). Pereira et al. described eight down regulated miRNAs (miR-26a, miR-29a, miR-99a, miR-143, miR-145, miR-199a,

miR-203, miR-513) and five upregulated miRNAs (miR-148a, miR-302b, miR-10a, miR-196a, and miR-132) in low SIL, high SIL and cervical SCC in comparison with normal samples (110). Only five miRNAs (miR-106a, miR-197, miR-16, miR-27a, and miR-142-5p) were found specifically deregulated in pre-neoplastic lesions but not in cervical carcinoma (110). Subsequently, many research groups reported the identification of specific miRNA signatures during the transition from SIL to cervical cancer with variable results mainly due to the small sample size, the type of specimens (i.e., formalin fixed paraffin embedded vs. fresh biopsies), the number of miRNAs included in each panel (ranging from one to 7788 miRNAs) as well as the diverse methods used to quantify (37, 96, 111, 112).

TABLE 1 | miRNAs identified in cervical tissues, cell exfoliates, and mucus as well as in the serum of high grade SIL and cervical cancer patients.

Deregulated miRNAs*	HSIL**	Cervical Cancer	References
Up regulated miRNAs in tissue biopsies	<i>let-7; miR-10a-5p; miR-16-5p; miR21-5p; miR-25-5p; miR-26a; miR-29a; miR-29b; miR-29c; miR-30a; miR-34b; miR-34c-5p; miR-92a-3p; miR-101; miR-125a-5p; miR-135b; miR-143; miR-145; miR-196a-5p; miR-223; miR-338; miR-301b; miR-345; miR-424; miR-466; miR-512-5p; miR-518a</i>	<i>miR-20a-5p; miR-31-5p; miR-96-5p; miR-142-5p; miR-189-5p; miR-200b; miR-224-5p; miR-944; miR-1246; let-5p; miR-9-5p; miR-10a-5p; miR-15b; miR-16-5p; miR-17; miRNA-19a/b; miR-20b; miR-21-5p; miR-25-5p; miR-27a; miR-29a; miR-30a; miR-92a-3p; miR-92b; miR-93; miR-106a; miR-125b; miR-127; miR-130a; miR-133a; miR-133b; miR-135b; miR-141b; miR-145b; miR-146a; miR-150; miR-155; miR-181b; miR-182; miR-185; miR-196a-5p; miR-199a; miR-199a; miR-199b; miR-199-s; miR-203b; miR-205; miR-215; miR-221; miR-222; miR-223; miR-301b; miR-320a; miR-361-5p; miR-373; miR-378; miR-425-5p; miR-449; miR-451a; miR-466; miR-486-5p; miR-494; miR-500; miR-505; miR-519d; miR-543; miR-590-5p; miR-711; miR-720; miR-886-5p; miR-888; miR-892b; miR-944; miR-1290; miR-2392; miR-3147; miR-3162; miR-4484; miR-6852;</i>	(24, 36–62)
Down regulated miRNAs in tissue biopsies	<i>Let-7a; miR-22; miR-29a; miR-34a; miR-99a-5p; miR-100-5p; miR-129b-5p; miR-193a-3p; miR-199a-3p; miR-203; miR-205; miR-216-5p; miR-218-5p; miR-212; miR-221; miR-27a; miR-27b; miR-342; miR-376c-3p***; miR-433; miR-484; miR-636; miR-770-5p</i>	<i>Let-7a; Let-7b; Let-7c; Let-7g; miR-7; miR-10b; miR-17-5p; miR-22; miR-24; miR-26a; miR-27b; miR-29a; miR-29b; miR-30a; miR-30e; miR-34a; miR-99a-5p; miR-100-5p; miR-101; miR-103b; miR-107; miR-124-3p; miR-125a-5p; miR-125b; miR-129b-5p; miR-132; miR-133a; miR-138; miR-139-3p; miR-141; miR-142-3p; miR-143; miR-144; miR-145; miR-149; miR-152; miR-154; miR-181; miR-182; miR-183; miR-186; miR-187; miR-193a; miR-193b; miR-195; miR-199a-3p; miR-199b; miR-200b; miR-200c; miR-202; miR-203; miR-204; miR-205; miR-211; miR-212; miR-214; miR-216-5p; miR-218; miR-223; miR-296; miR-320; miR-326; miR-328; miR-329; miR-331-3p; miR-335; miR-337; miR-338-3p; miR-342; miR-362; miR-374c-5p; miR-375; miR-376c; miR-379; miR-383; miR-376a; miR-424; miR-429; miR-451; miR-484; miR-486-3p; miR-489-3p; miR-491-5p; miR-494; miR-497; miR-503; miR-506; miR-544; miR-630; miR-634; miR-638; miR-720; miR-758; miR-892b; miR-1297; miR-1246; miR-2861; miR-3185; miR-3156-3p; miR-3666; miR-3960; miR-4262; miR-4467; miR-4488; miR-4525</i>	(24, 36, 37, 39, 40, 55, 58, 63–93)
Up regulated miRNAs in cervical exfoliated cells	miRNA-16-2; miRNA-20a		(94)
Down regulated miRNAs in exfoliated cervical cells	miR-424; miR-375; <i>miR-34a</i> ; miR-218; miRNA-195; miRNA-29a	miR-758	(93–95)
Up regulated miRNAs in the serum		<i>miR-20a-5p</i>	(39, 59, 61, 96–103)
	<i>miR-9-5p; miR-10a-5p; miR-20a-5p; miR-92a-3p; miR-196a-5p;</i>	miR-9-5p; miR-21-5p; miR-29a-3p; <i>miR-92a-3p;</i> miR-101-3p; miR-122-5p; miR-132-3p; miR-141-3p; miR-150; miR-155; miR-191-5p; <i>miR-196a-5p;</i> miR-200c-3p; miR-203a-3p; miR-205-5p; miR-212-3p; miR-214-3p; miR-370; miR-425-5p; miR-486-5p; miR-494; miR-1246	
Down regulated miRNAs in the serum	Let-7a-5p; miR-101; miR-142-3p	Let-7a-5p; miR-17-5p; miR-24; miR-101; miR-103a-3p; miR-106a-5p; miR-106a-5p; miR-139-3p; miR-142-3p; miR-144-3p; miR-191-5p; miR-195-5p; miR-212-3p; miR-218-5p; miR-370; miR-425-5p; miR-451a; miR-758	(93, 99, 102, 104–106)
Up regulated miRNAs in cervical mucus	Let-7a-5p; <i>miR-10a-5p;</i> miR-21-5p; miR-141-3p; miR-144-3p; miR-155-5p; miR-205-5p; miR-451a	Let-7a-5p; miR-10a-5p; miR-17-5p; miR-21-5p; miR-106a-5p; miR-141-3p; miR-144-3p; miR-155-5p; miR-205-5p; miR-451a; miR-758;	(96)
Down regulated miRNAs in cervical mucus	Not reported	Not reported	

*miRNAs up-regulated or down regulated in more than one study as determined by Pardini et al. (37) have been highlighted in bold; miRNAs with statistically significant expression changes in cervical neoplasia samples vs. normal epithelia as reported by He et al. (24) have been written in italics; miRNAs which have been found specifically expressed in in cervical cancer and not in HSIL are underlined and listed as a separated group.

**HSIL group comprises CIN2-3 lesions.

***The miR-376c-3p has been found significantly down regulated in CIN3 compared to CIN2 (24).

He et al. performed a systematic study to identify miRNAs with statistically significant expression changes among 827 CIN and 3,095 cervical carcinomas as well as 2,099 non-tumor tissues from 85 selected studies (24). All studies analyzing miRNA profile in human cancerous and non-cancerous cervical tissues were included in such analysis. This approach allowed to identify 42 up regulated and 21 down-regulated miRNAs in different stages of cervical neoplasia. In particular, seven miRNAs (miR-29a, miR-34a, miR-99a-5p, miR-100-5p, miR-199a-3p, miR-203, and miR-218-5p) were found down-regulated and five miRNAs (miR10a-5p, 16-5p, 25-5p, 92a-3p, and 196a-5p) up regulated in CIN1 as well as in CIN 2–3 and cervical SCC compared to cervical non-tumor tissues. In CIN2-3 there were eight additional down regulated miRNAs and 27 new upregulated miRNAs with the miR-376c-3p specifically down regulated in CIN3 compared to CIN2. The functional target of miR-376c-3p is the BMI1 polycomb ring finger proto-oncogene which is highly expressed in several cancer types, including cervical cancer (113). Thus, the miR-376c-3p and the BMI1 factor may represent novel biomarkers for diagnosis as well as for target therapy in cervical cancer patients. Moreover, five new down regulated (miR-1, miR-99b-5p, miR-126-3p, miR-140-5p, miR-196b-5p) and ten additional up-regulated miRNAs (miR-20a-5p, miR-31-5p, miR-96-5p, miR-142-5p, miR-189-5p, miR224-5p, miR-200b, miR-944, miR-1246, and Let-5p) were identified in cervical carcinoma compared to CIN3 miRNA profile (24). Among these, miR-96-5p and miR-126-3p, which are predicted to target PTEN and MARK1 tumor-associated genes, have shown to be associated with metastatic potential of cervical cancer and to have a great potential as prognostic biomarkers or therapeutic targets (114, 115).

The expression levels of miRNAs consistently altered in all stages of cervical neoplasia may be directly deregulated by early viral proteins produced soon after infection. Gocze et al. performed the miRNA profiling of cervical neoplasia biopsies and identified the over expression of miR-21, miR-34a, miR-196a, miR-27a, and miR-221 as specific signature of HPV positivity irrespective of the clinical tumor grading (38). Indeed, the E6 protein encoded by oncogenic HPVs has shown to down regulate both the tumor suppressors miR-34a, through the viral E6-mediated degradation of the oncosuppressor p53 (116, 117), and the miR-218, in a p53-independent manner thus causing over expression of its target laminin 5 β 3 (LAMB3) gene in cervical SCC cells (63, 118). Furthermore, the HPV E6 was demonstrated to up regulate miR-20a thereby enhancing cell proliferation, through the AKT/p38 pathway activation, and tumor growth by down regulation of the target gene PDCD6 (119). The E6 protein has also shown to increase miR-20b levels which in turn inhibits metastasis suppressor TIMP-2 expression and promotes epithelial-mesenchymal transition, migration and invasion of cervical cancer cells (120). Both E6 and E7 oncoproteins have shown to strongly suppress miR-424 levels in HPV16 and HPV31-positive cells causing increased expression of its target gene CHK1 encoding a damage repair factor (25).

Integration of HPV DNA into host genome, with disruption of E2 viral gene and host chromosomal loci, is a critical event in cancer development and progression. Interestingly, the viral status has shown to affect the levels of several

miRNAs. Mandal et al. reported that cervical cancer biopsies either carrying integrated or episomal HPV16 genomes have a common expression signature of miR-200a associated with HPV16 genotype. Conversely, down regulation of miR-181c and expression of its target gene CKS1B was observed only in cases harboring HPV16 episomes but not in cancer tissues with the integrated virus (121). Therefore, miR-200a and miR-181c could represent useful biomarkers of cervical neoplasia progression if will be validated in clinical studies.

The HPV genome encodes the HPV-16-miR-H1-1 and HPV-16-miR-H2-1 which, besides being essential for viral infection and maintenance, are able to target critical cell genes, including those regulating cell cycle progression, migration, and immunological response (122). On the other hand, the miR-375 has shown to suppress HPV E6 and E7 expression and to induce increased levels of p53 and p21, higher activity of caspase-3 and caspase-9, suppression of E6AP, IGF-1R, cyclin D1, and survivin protein expression (123). Development of therapeutic strategies able to increase miR-375 levels and re-expression of tumor suppressors may be effective to improve the clinical outcomes in cervical cancer patients.

Recently, Pardini et al. performed a comprehensive evaluation of those miRNAs found deregulated in more than one study in order to identify consistent signatures occurring during the progression from normal cervical epithelium to SIL stages and cervical SCC. Among the 24 studies included in the analysis 17 and 13 miRNAs were found up or down regulated, respectively, in relation to cervical carcinoma progression (37). Among the over expressed miRNAs, one (miR-21) was found associated with cervical carcinogenesis in five studies, and nine (miR-9, miR-16, miR-25, miR-10a, miR-20b, miR-31, miR-92a, miR-106a, and miR-155) in three studies. Among under expressed miRNAs, miR-218 was described in six studies, miR-375 and miR-203 in four studies and six miRNAs (miR-99a, miR-29a, miR-195, miR-125b, miR-34a, and miR-100) in three studies. These findings suggest that specific panels including commonly deregulated miRNAs may serve as effective diagnostic biomarkers for early diagnosis and disease progression as well as for therapy in cervical cancer patients.

Identification of novel cancer biomarkers in cervical exfoliated cells as well as biological fluids may have an important role in early cancer detection and/or recurrence monitoring following therapy. Interestingly, Tian et al. showed that the expression level of miR-424, miR-375, miR-34a, and miR-218 in cervical exfoliated cells was statistically significant lower in high grade lesions than in low-grade lesions with a sensitivity superior to the cytology, suggesting that their detection may provide a new triage choice for the follow up of HPV-positive women (95). Moreover, the levels of miR-34a, miR-125, and miR-375 were also found deregulated in cervical exfoliated cells in association with cancer progression (37). Accordingly, Ye et al. observed that the relative low expression of miRNA-195 and miRNA-29a and the high expression of miRNA16-2 and miRNA20a in the cervical exfoliated cells was predictive of high grade SIL in the women group diagnosed with low grade SIL. Among these, miR-29a expression achieved the highest sensitivity (92.6%) and specificity (80.7%) in the identification of high grade SIL (94). These results indicate that miRNA expression profiles may

represent promising biomarkers for the early diagnosis of high grade cervical lesions and cervical cancer.

Profiling of miRNAs in cervical mucus has also shown to be a good strategy for the identification of cervical neoplastic lesions (96). Indeed, four miRNAs (miR-126-3p, miR-20b-5p, miR-451a, and miR-144-3p) detected in cervical mucus have been shown effective for diagnosis of cervical adenocarcinoma and high-grade intraepithelial lesions. However, more investigations are needed in order to establish the clinical value of miRNA detection in cervical mucus.

Few studies evaluated the parallel expression of miRNAs in cervical cancer biopsies and in serum samples and the potential of circulating miRNAs as cancer biomarkers. Chen et al. examined the levels of 1,450 miRNAs in cervical carcinoma tissues as well as in sera and identified 62 up regulated and 27 down regulated in comparison with normal controls (39). Among these, the miR-1246, miR-20a, miR-2392, miR-3147, miR-3162-5p, miR-4484, and miR-4667-5p were all over expressed in patients sera consistently with their high levels in cervical cancer tissues (39). More recently, Shukla et al. identified 14 miRNAs differentially expressed in cervical cancer tissue and serum specimens by performing sequencing analysis and real time PCR (124). Among them, miR-17-5p, miR-32-5p, and miR-454-3p were over expressed while miR-409-3p was down regulated both in serum samples and tumor biopsies of cervical cancer patients. Moreover, an inverse correlation was observed between the miR-409-3p and miR-454-3p levels and the expression of their target genes MTF2 and ST18, respectively, in cervical cancer biopsies. The MTF2 is a polycomb-like (PCL) protein which, in association with the polycomb repressive complex 2 (PRC2), mediates transcriptional repression and regulates several biological processes including cell differentiation (125). The ST18 genes has shown to inhibit colony formation of cancer cells in soft agar and to regulate pro-apoptotic and pro-inflammatory gene expression in fibroblast and in pancreatic B-cells (126, 127). Further studies need to be performed to fully characterize the role of such genes in cervical carcinogenesis.

Few studies investigated the expression of specific circulating miRNAs in distinct stages of cervical carcinoma. Yu et al. detected lower levels of miR-218 in cervical cancer patients sera compared to healthy women matched by age. Importantly such reduction was significantly associated with lymph node metastasis suggesting its potential use as circulating prognostic marker for cervical cancer invasion and metastasis (104). Several other circulating miRNAs have been proposed to be predictive of lymph node metastasis in patients with early stages cervical cancer (39, 97, 128). Among these, promising candidate biomarkers for their limited variations between tumor tissue and serum are represented by miR-1246, miR-20a, miR-2392, miR-3147, miR-3162-5p and miR-4484 (39).

DEREGULATED lncRNAs IN CERVICAL CANCER

lncRNAs have the ability to bind proteins, mRNAs or miRNAs, are involved in multiple biological functions and have an

important role in cancer development. Several lncRNAs, including HOTAIR, H19, MALT1, CCAT2, SPRY4-IT1, GAS5, CCHE1, MEG3, LET, EBIC, and PVT1, are recognized to play crucial functions in cervical cancer progression, invasion and metastasis as well as in radio-resistance [Table 2; (29, 165)].

The 2.2 kb HOX transcript antisense intergenic RNA, namely HOTAIR, is a lncRNA encoded by the antisense strand of the HOXC gene located in the chromosome 12 q13.13 (166). Similarly to other lncRNAs, HOTAIR has shown to recruits chromatin-modifying proteins and to affect cancer epigenome modulation (81, 167). Indeed, the HOTAIR 5' domain binds the zeste homolog 2 (EZH2) and concurs to the silencing of the target gene nemo-like kinase (NLK) (168). In cervical cancer HOTAIR levels have shown to be strictly controlled by the HPV E7 protein (129). Furthermore, HOTAIR has shown to act as sponge for several miRNAs and to cause deregulation of the respective target genes. Indeed, HOTAIR has shown to alter the miR-143-3p/BCL2 axis favoring cervical cancer cell growth (130) and miR-23b/MAPK1 axis contributing to cell proliferation and metastasis (139). Moreover, the over expression of HOTAIR has demonstrated to regulate diverse metabolic functions such as the activation of mTOR pathway in cervical carcinoma cell lines HeLa, CaSki, and C33A (131), as well as the activation of Notch-Wnt signaling in SiHa cells (132). HOTAIR expression causes the up regulation of the vascular endothelial growth factor (VEGF), matrix metalloproteinase-9 (MMP-9) and EMT-related genes thus promoting tumor aggressiveness in cervical carcinoma (133). HOTAIR levels have observed to be consistently high in cervical cancer tissues and associated with lymph node metastasis and reduced overall survival (133). Moreover, the HOTAIR levels are higher also in the serum of cervical cancer patients and significantly associated with increased tumor size, lymph vascular space invasion, lymph node metastasis, and reduced survival (132). These data indicated that HOTAIR might represent a novel diagnostic circulating biomarker as well as a promising therapeutic target in cervical cancer. The single nucleotide polymorphism rs920778 T located in the HOTAIR enhancer has shown to be associated with elevated expression of HOTAIR and with cancer susceptibility (169). In addition, the frequency of the rs920778 C HOTAIR allele is reported to be significantly higher in HPV-positive cervical cancer cases while its expression level is observed to be low due to the ability of miR-22 to bind rs920778 C sequence and to suppress the HOTAIR expression (170).

The lncRNA H19, encoded by the H19 gene located in the chromosome loci 11p15.5, is expressed only from the maternally-inherited chromosome (171). It was the first lncRNA identified as a riboregulator and shown to be expressed in fetal tissues and adult muscles as well in many kinds of cancer (172, 173). The lncRNA H19 is modulated by the HPV16 E6 oncoprotein and demonstrated to act as a molecular sponge for miR-138-5p in epithelial cells (160, 174). Kim et al. reported that the lncRNA H19 which is abnormally expressed in cervical cancer may be associated with the cervical cancer progression (140).

The metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), first identified in non-small cell lung cancer, is an 8,000 nucleotides lncRNA located in the chromosome

TABLE 2 | lncRNAs that are reported to have oncogenic or tumor suppressor functions in cervical cancer.

lncRNAs	Function	Sponged miRNAs	Deregulated pathways in cervical cancer	References
HOTAIR	Oncogenic	miR-22, miR-23b, miR-143-3p	BCL2, PRC2, LSD1, VEGF, mmp-9, mTOR, Notch, Wnt, STAT3, wnt/ β -catenin, PI3K/AKT, HPV E7 oncoprotein	(129–139)
H19	Oncogenic	miR-138-5p	IGF2, HPV E6 oncoprotein	(140)
MALAT1	Oncogenic	miR-124, miR-145, miR-206	RBG2, E-cadherin, β -catenin, vimentin, ZO-1, caspase-3, caspase-8, Bax, Bcl-2, and BclxL	(141)
CCAT2	Oncogenic	miR-17-5p, miR-20a	MYC, wnt in colon cancer	(142)
SPRY4-IT1	Oncogenic	miR-101-3p	ZEB1, EMT, E-cadherin, vimentin	(143)
GAS5	Oncosuppressive	miR-106b	IER3	(144)
CCHE1	Oncogenic		PCNA, ERK/MAPK	(145, 146)
MEG3	Oncosuppressive	miR-21-5p		(147)
LET	Oncosuppressive		LIN28	
EBIC	Oncogenic		EZH2, Wnt/ β -catenin, E-cadherin	(148, 149)
PVT1	Oncogenic	miR-200, miR-424, miR-195	EZH2, Myc, Nop2, p15, p16, H3K27me3, NF- κ B	(150–157)
LINC00675	Oncogenic		Wnt/ β -catenin, Bax and GSK-3 β Bcl-2	(158)
C5orf66-AS1	Oncogenic	miR-637	RING1	(159)
FAM83H-AS1	Oncogenic		HPV E6, E6-p300	(160)
CCAT1	Oncogenic	miR-181a-5p	MMP14	(161)
NOC2L-4.1	Oncogenic	miR-630	YAP1	(162)
PAX8 AS1	Oncosuppressive		PAX8, NOTCH1 (pancreatic carcinoma)	(163)
RSU1P2	Oncogenic	let-7a	IGF1R, N-myc	(164)

11q13.1. MALAT1 has shown to promote epigenetic changes and to modulate gene expression, nuclear organization as well as regulation of alternative splicing by acting as decoy for splicing factors (175). It is found largely expressed in many cancer types in relation to the accumulation of aberrant splicing products (176). The MALAT1 is over expressed in cervical cancer cell lines and cancer tissues infected with high risk HPVs (177), acts as a sponge for several miRNAs, including miR-124, miR-145, and miR-206, and favors cervical cancer progression (178). Accordingly, down regulation of MALAT1 in cervical cancer cell lines and in cervical cancer tissues reduces invasion and metastasis through the inhibition of epidermal mesenchymal transition and modulation of the MALAT1-miR-124-RBG2 axis (141). The sponging of miR-145 by MALAT1 has suggested to be involved in the mechanisms of radio-resistance in cervical cancer radiotherapy (178). Moreover, MALAT1 expression has recognized to be an independent prognostic factor in addition to tumor size, FIGO stage, and lymph node metastasis (179). The knockdown of MALAT1 in CaSki cell line caused decrease of cell cycle regulators, such as cyclin D1, cyclin E, and CDK6, leading the cells to accumulate in G1 phase (180).

lncRNA colon cancer-associated transcript 2 (CCAT2) is a 1,752 nucleotide sequence located in the chromosome 8q24 and expressed in microsatellite-stable colorectal cancers (181). Next, CCAT2 has shown to be over expressed and defined as biomarker of poor prognosis in gastric, bladder, non-small cell lung, small cell lung, breast, and ovary cancers as well as in esophageal squamous cell carcinoma and glioma (182). CCAT2 has found to be up regulated in HeLa, CaSki, and SiHa cervical cancer cells as well as in cervical cancer tissues (183). The inhibition of CCAT2 expression by siRNA in cervical cancer cells has

shown to suppress cell proliferation. In cervical cancer patients the high expression of CCAT2 is correlated to advanced FIGO stage, lymph node metastasis, deep cervical invasion and reduced survival (183). However, the molecular mechanism mediating the activity of CCAT2 in cervical cancer remain uncharacterized.

SPRY4 intronic transcript 1 (SPRY4-IT1) derives from the intron two of the SPRY4 gene and has shown to act as an oncogenic factor or a tumor suppressor in different cancer types (19, 184). Indeed, it is reported to be over expressed in melanoma, non-small cell lung, esophageal cancer and under expressed in gastric cancer (19, 185, 186). The expression levels of SPRY4-IT1 have been found higher in cervical cancer than in normal tissues and associated with advanced clinical stages and shorter overall survival of cervical cancer patients (187). More recently, the silencing of SPRY4-IT1 in cervical cancer cell lines has shown to inhibit migration and invasion through the SPYR4-IT1/miR-101-3p/ZEB1 axis. This effect is associated with suppression of EMT changes, increased E-cadherin levels and decreased the N-cadherin and vimentin expression (143).

Growth arrest-specific transcript 5 (GAS5) is 651 nucleotide lncRNA encoded by a sequence located in the chromosome 1q25 (188). GAS5 has tumor suppressor activity in several cancer types (189). Accordingly, its decreased expression has a strong association with tumor development and worse clinical outcome in cervical cancer patients (190). Moreover, inhibition of GAS5 in cervical cancer cells has shown to increase the proliferation, migration and invasion confirming its oncosuppressor activity in the cervical cancer progression (190). Gao et al. reported that GAS5 acts as miR-106b sponge causing up regulation of IER3 expression and enhanced radio-sensitivity of cervical cancer cells (144).

Cervical carcinoma high-expressed 1 (CCHE1) lncRNA is 2,500 nucleotide sequence transcribed from a region located in the chromosome 10. It is over expressed in cervical cancer in association with advanced tumor stages, increasing tumor size, invasion and poor prognosis (191). The CCHE1 has demonstrated to bind and stabilize the mRNA of proliferating cell nuclear antigen (PCNA) thus promoting its over expression and increased cervical cancer cell proliferation (145). Peng and Fan, demonstrated that CCHE1 inhibition causes inactivation of the ERK/MAPK pathway, growth arrest and apoptosis (146).

Maternally expressed gene (MEG3) is a 1,600 nucleotide lncRNA derived from the DLK1-MEG3 locus located on the chromosomal region 14q32.3, first identified as the ortholog of gene trap locus 2 (Gtl2) in mice (192). MEG3 is expressed in many normal tissues and its loss has been reported in many cancer types. The over expression of MEG3 can inhibit proliferation and increase apoptosis in cancer cells either in a p53 dependent or independent manner (193). Expression of MEG3 is low both in cervical cancer tissues and in cervical cancer cell lines. Increased levels of MEG3 in cervical cancer cell lines have shown to inhibit cell proliferation, induce cell cycle arrest and cause apoptosis (194). MEG3 has shown to act as a cancer suppressor through its ability to down regulate the miR-21-5p levels in cervical cancer cell lines (147). Indeed, knockdown of MEG3 in HeLa and CaSki cells induced significant up regulation of miR-21-5p expression (147). Thus, could act as a tumor suppressor able to inhibit tumor growth in cervical cancer.

lncRNA-Low Expression in Tumor (LET), is a 2,600 nucleotide long RNA transcribed from a region located in the chromosome locus 15q24.1. It is down-regulated in hepatocellular, gallbladder, esophageal and cervical carcinoma (182, 195). In cervical cancer patients has been reported a significant correlation between LET expression levels and clinicopathological parameters suggesting that it might be considered a prognostic biomarker if confirmed by more clinical studies (196).

EZH2-binding lncRNA (EBIC) is a 1,500 nucleotide RNA encoded by a sequence located in the chromosome locus 12q22. The over expression of EBIC has shown to deregulate the Wnt/ β -catenin signaling pathway and to promote cell proliferation, invasion and migration as well as to increase cisplatin resistance in ovarian cancer (148). EBIC has been described as an oncogenic lncRNA also in cervical cancer, indeed it was demonstrated to promote tumor cell invasion by binding to EZH2 and inhibiting E-cadherin expression (149).

Plasmacytoma variant translocation 1 (PVT1) is a highly conserved lncRNA, which is located downstream of MYC gene and is frequently co-amplified with MYC in several cancer types (150–152, 193). Iden et al. utilized siRNA and LNA-mediated knockdown to analyze the effect of reduced levels of PVT1 in cervical cancer cells obtaining inhibition of cell proliferation, migration, invasion and cisplatin resistance (153). Furthermore, PVT1 has shown to decrease miR-195 and miR-200b expression in cervical cancer either by enhancing histone H3K27me3 in the miR-195 and miR-200b promoters or by direct binding of miR-195 and miR-200b (154, 155). MiR-195 is associated with epithelial-mesenchymal transition and chemo resistance, whereas miR-200b is associated with cell proliferation, invasion

and migration of cervical cancer cells. Yang et al. reported that serum levels of PVT1 positively correlate with PVT1 expression in cancer tissues indicating that it could serve as a biomarker for diagnosis of cervical cancer (156).

Along with the above-mentioned lncRNAs, many other novel sequences, such as LINC00675, C5orf66-AS1, FAM83H-AS1, CCAT1, NOC2L-4.1, PAX8 AS1, and RSU1P2, have identified as playing multiple roles in cervical tumorigenesis (Table 2). Their ability to sponge specific miRNAs and to deregulate metabolic pathways have been mainly investigated in cell culture models. Therefore, clinical studies are needed to determine the possible use of these novel lncRNAs as biomarkers for diagnosis and prognosis of cervical cancer.

CIRCULAR RNAs IN CERVICAL CANCER

CircRNAs are highly expressed in many cancer types, such as breast, lung and colorectal cancer (197–200). Several circRNAs are abnormally expressed in cervical cancer tissues as well as derived cell lines and contribute to tumorigenesis mostly by sequestering miRNAs [Table 3; (34)]. Among these, hsa_circ_0141539 (circRNA-000284), encoded by the Clorf116 gene, was found significantly over expressed in cervical cancer tissues compared to adjacent non-tumor tissues and directly associated with tumor size, FIGO stage as well as myometrium invasion (202). The hsa_circ_0141539 is able to sponge miR-518d-5p/519-5p causing increased expression of the target gene CBX8 and promotion of malignant transformation of cervical cells (202). This circRNA was also demonstrated to sponge miR-506 causing an increased expression of Snail-2 which is a direct target of miR-506 (201). Silencing of hsa_circ_0141539 has been proposed as a novel treatment strategy for cervical cancer patients.

The circRNA Hsa_circ_0023404, derived from the RNF121 gene located on the chromosome 11, was significantly over expressed in cervical cancer and associated with poor prognosis (203). Hsa_circ_0023404 has shown to sequester miR-136 thus promoting over expression of target gene TFCP2, consequent activation of YAP signaling pathway and consequent cervical cancer development and progression (203). More recently, Guo et al. reported a novel biological effect of hsa_circ_0023404 relying on the subtraction of miR-5047 with consequent induction of VEGFA expression and increased cervical cancer metastasis and chemoresistance. Moreover, hsa_circ_0023404 and VEGFA were found concordantly up regulated in cervical tumors, while miR-5047 was under expressed (213).

Gao et al. performed a microarray analysis of 35 cervical cancer cases and identified 45 significantly up regulated circRNAs with hsa_circ_0018289 as the most deregulated (35). Hsa_circ_0018289 was observed to directly bind miR-497 causing increased cell proliferation, migration and invasion of cervical cancer cells (35). Thus, hsa_circ_0018289, similarly to other circRNA, has demonstrated to have an oncogenic role in cervical cancer development. Cai et al. reported that also hsa_circ_0000263 has an oncogenic role being significantly up regulated in cervical cancer cells, able to bind miR-150-5p

TABLE 3 | CircRNA that were reported to be deregulated in cervical neoplasia.

CircRNAs	Targets	Effect in cervical cancer and/or cell lines	References
Hsa_circ_000284	miR-506, Snail-2	Promote proliferation and invasion	(201)
Hsa_circ_0141539	miR-518d-5p, miR-519-5p, CBX8	Promote proliferation, migration and invasion	(202)
Hsa_circ_0023404	miR-136, TFCP2, YAP	Promote proliferation and invasion	(203)
Hsa_circ_0018289	miR-497	Promote cell proliferation, migration and invasion	(35)
Hsa_circ_0000263	miR-150-5p, MDM4, p53	Promote cell proliferation, migration	(204)
Hsa_circ_0001445	miR-620	Suppress proliferation and invasion	(205)
Hsa_circRNA_101996	miR-8075, TPX2		
Hsa_circ_0031288	HuR, PABPN1	Decrease cell proliferation	(206)
Hsa_circ_0004015	miR-1183, and PDPK1	Promote cell migration, angiogenesis and radio-resistance	(207)
CircATP8A2	miR-433, EGFR	Promote cervical cancer progression	(208)
Circ_0067934	miR-545	Promote cervical cancer progression	(209)
CircEIF4G2	miR-218, HOXA1	Promote cell proliferation and migration	(210)
CircCLK3	miR-320a, FoxM1	Promote cervical cancer progression	(211)
CircE7	pRb	HPV encoded circular E7 RNA promoting cell transformation	(212)

and to promote cell proliferation and migration through the hsa_circ_0000263/miR-150-5p/MDM4/p53 regulatory network affecting p53 activity (204). Conversely, the hsa_circ_0001445 (circSMARCA5) is able to sponge the miR-620 and to act as an oncosuppressor being its expression decreased in cervical cancer cells and its over expression causing inhibition of cell proliferation, invasion and migration (205).

Very recently, Song et al. by performing *in silico* analyses detected higher expression of hsa_circRNA_101996 in cervical cancer and observed a correlation with tumor stage, tumor size, lymph node metastasis, and poor outcomes (214). The oncogenic activity of hsa_circRNA_101996 has shown to be mediated by sequestration of miR-8075 and deregulation of TPX2 gene expression which represents a new mechanism of cervical cancer development (214). Others up regulated circRNAs in cervical cancer cells are circATP8A2 promoting cervical cancer progression through the circATP8A2/miR-433/EGFR axis, and circ_0067934 which binds miR-545 and is associated with advanced cancer stage, lymph node metastasis, and poor prognosis (208, 209). Moreover, Mao et al. identified the circEIF4G2 as over expressed in cervical cancer cells and able to interact with miR-218 causing enhancement of cervical cancer progression through the circEIF4G2-miR-218/HOXA1 axis (210). Recently, the circCLK3, which is a novel circRNA found over expressed in cervical carcinoma, has demonstrated to sponge miR-320a and to abolish its ability to suppress FoxM1 transcription factor expression as well as to promote cell proliferation, epidermal mesenchymal transition, migration, and invasion of cervical cancer cells (211). A recent study evaluating the expression profile of circRNAs by high-throughput RNA sequencing in three HPV16 positive cervical cancer cases identified 99 deregulated circRNAs (58 over expressed and 41 under expressed circRNAs) of which 44 have not been previously described and their role in cancer has not yet established (215). All these findings clearly show that many circRNAs play key roles in cervical cancer development and that they can be used as novel diagnostic and prognostic biomarkers as well as for

targeted therapies. However, more studies are needed to establish their significance as biomarkers of early disease and clinical outcome indicators.

High risk HPVs have recently demonstrated to encode a circRNA encompassing the E7 oncogene (circE7) (212). Such viral circRNA has shown to be modified by the N6-methyladenosine (m6A), to localize in the cytoplasm, to associate with polysomes, and to produce E7 oncoprotein. CircE7 is expressed in HPV16 positive CaSki cells and its targeted disruption causes reduction of E7 oncoprotein levels and cell growth inhibition (212). These results provide evidence of a new molecular mechanism of viral related tumorigenesis in HPV-related human malignancies and the possibility to search for new types of viral nucleic acids in order to discriminate progressing vs. regressing cervical lesions.

CONCLUSION

The discovery of aberrantly expressed miRNAs, lncRNAs, and circRNAs in cervical cancer have defined new molecular mechanisms of cervical cancer tumorigenesis and provided considerable opportunities for translating the non-coding RNAs research into clinical settings. Data from emerging studies clearly highlight the significance of specific miRNA signatures in the diagnosis and prognosis of cervical cancer. Particularly, miRNAs with oncogenic potential differently expressed in different stages of cervical cancer and those associated with high risk HPV infection might represent promising biomarkers for oncologic screening and cancer recurrence monitoring. Indeed, the analysis of specific miRNA panels have demonstrated a greater diagnostic value, higher sensitivity and specificity, in patients with cervical lesions and cancer. More importantly, circulating miRNAs appear valuable for the early detection of cervical cancer and for monitoring the clinical outcome of advanced cancer considering that the majority of cancer associated deaths are caused by metastases to distant organs. In addition, miRNA testing may reduce the need for invasive

cervical biopsies and are useful in predicting the prognosis of cervical cancer. However, larger studies are required to validate miRNA assays as diagnostic marker in comparison with cytology and HPV screening methods. Several molecules able to target oncogenic miRNAs have been developed such as the synthetic antisense oligonucleotides encoding miRNA complementary sequences. Hypomethylation agents such as decitabine or 5-azacitidine have also shown effective to induce epigenetic silencing of miRNAs and they are the approved treatments for downregulating the expression of several non-coding RNAs and mRNAs in myelodysplastic syndromes. Therefore, such therapeutic approaches, although in the early stage of clinical translation, might become effective drugs providing insight into the treatment of all types of cancers.

lncRNAs are important as potential biomarkers for cervical prognosis, invasion, metastasis, chemo-radio-resistance. Several lncRNAs can be detected in the serum and other biological fluids. Indeed, circulating HOTAIR, MALAT1, and MEG3 transcripts were found significantly higher in cancer patients compared to healthy subjects suggesting their potential as diagnostic biomarkers. Moreover, the increased HOTAIR levels in the serum of cervical cancer patients is also indicative of the metastatic tumor phase, adenocarcinoma, lymphatic node metastasis and tumor recurrence. The molecular mechanisms of lncRNAs in cervical cancer need further characterization. Particularly the interplay with miRNAs and circRNAs needs to be fully discovered. Inhibition of the oncogenic activity of lncRNAs is also in the early phase of research since no RNA-interference drugs have been approved for clinical use.

CircRNAs have been recently discovered and their role in cervical cancer pathogenesis recognized. Massive parallel sequencing and bioinformatics techniques allowed uncovering many circRNAs differentially expressed in cervical cancer tissues compared to normal cells suggesting that they have relevant roles in this cancer type. Their activity is mainly mediated by the sponging of specific miRNAs. The study of circRNAs potentially represents a new promising strategy for diagnosis and treatment of cervical cancer. However, the characterization of biological functions of circRNAs in cancer cells is in a nascent stage and most activities have not been fully elucidated.

More studies mainly based on high-throughput sequencing technologies, which simultaneously evaluate the network of miRNAs, lncRNAs, and circRNAs are needed to further reveal the complexity of the interplay between diverse classes of non-coding RNAs and deregulation of new actionable metabolic pathways for treatment of cervical cancer.

AUTHOR CONTRIBUTIONS

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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