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REVIEW

LncRNAs: key players and novel insights into cervical cancer

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Abstract Cervical cancer contributed the second highest number of deaths in female cancers, exceeded only by breast cancer, carrying high risks of morbidity and mortality. There was a great need and urgency in searching novel treatment targets and prognosis biomarkers to improve the survival rate of cervical cancer patients. Many long non-coding RNAs (lncRNAs) were emerging as pivotal regulators in various biological processes and took vitally an effect on the oncogenesis and progression of cervical cancer. In this review, we summarized the origin and overview function of lncRNAs; highlighted the roles of lncRNAs in cervical cancer in terms of prognosis and tumor progression, invasion and metastasis, apoptosis, and radio-resistance; and outlined the molecular mechanisms of lncRNAs in cervical cancer from the aspects of the interaction of lncRNAs with proteins/mRNAs (especially in HPV protein) and miRNAs, as well as RNA N-methyladenosine (m6A) methylation of lncRNAs. Meanwhile, the application of lncRNAs as biomarkers in cervical cancer prognosis and predictors for metastasis was also discussed. An overview of these researches will be valuable for broadening horizons into mechanisms, selection of meritorious biomarkers for diagnosis as well as prognosis, and future targeted therapy of cervical cancer.

Keywords LncRNA · Cervical cancer · Dysregulation · Function · Mechanism · ceRNA · EMT · EZH2 · GAS5 · HOTAIR · LncRNA-ANRIL · LncRNA-CCHE1 · LncRNA-EBIC · LncRNA-LET · m6A · MALAT1 · MEG3 · NEAT2 · TUSC8 · Xist

Abbreviations

AUC	Areas under the ROC curve
ceRNA	Competing endogenous RNA
lncRNA-CCHE1	Cervical carcinoma high-expressed lncRNA 1
EMT	Epithelial-mesenchymal transition
EZH2	Enhancer of zeste homolog 2
GAS5	Growth arrest-specific transcript 5
HOTAIR	Hox transcript antisense intergenic lncRNA
LincRNA	Long intergenic non-coding RNA
LncRNAs	Long ncRNAs
lncRNA-ANRIL	lncRNA-antisense non-coding RNA in the INK4 locus
LncRNA-EBIC	EZH2-binding lncRNA in cervical cancer
LncRNA-LET	lncRNA low expression in tumor

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m6A	N-Methyladenosine
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
MEG3	Maternally expressed gene 3
MMP-9	Matrix metalloproteinase-9
MREs	miRNA response elements
ncRNAs	Non-coding RNAs
NEAT2	Nuclear-enriched transcript 2
PCNA	Proliferating cell nuclear antigen
VEGF	Vascular endothelial growth factor
VIM	Vimentin
SCARLET	Site-specific cleavage and radioactive-labeling followed by ligation-assisted extraction and thin-layer chromatography
TUSC8	Tumor suppressor candidate 8
Xist	X inactive-specific transcript

Introduction

Protein-coding genes accounted for just 2 % of the human transcription product, while the preponderance of transcripts were non-coding RNAs (ncRNAs) containing long ncRNAs (lncRNAs) [1]. The ENCODE project have implied that 76 % of the human genome was transcribed to generate a series of lncRNAs [2, 3]. LncRNAs were broadly described as RNAs over 200 nucleotides (nt) in length, which possessed a lot of structural features of the mRNAs, containing a poly(A) tail, a 5′-cap, and a promoter structure, whereas owned no conservative open reading domain [4, 5]. They were lack of protein coding capacity and could be localized to the nucleus as well as cytoplasm [6]. With the utilization of the high-throughput sequencing and other emerging research technologies, the bio-functions of lncRNAs were gradually getting to be comprehended [7]. Accumulating evidence suggested that lncRNAs function in a broad range of cellular processes, containing cell growth, survival, migration, invasion, differentiation, and so on [8–10]. However, the bio-functions and molecular mechanisms of lncRNAs in human diseases and cancers in particular remained largely unknown [11]. More efforts should be made to explore the lncRNAs world.

As one of the most common malignant gynecological tumors, cervical cancer was responsible for 10–15 % of all female cancer-related deaths worldwide that contributed the second highest number of deaths in female cancers, exceeded only by breast cancer [12–14]. At the time of diagnosis, 80 % patients have developed into invasive cancer, and the age at diagnosis was slowly decreasing. Moreover, cervical cancer still carried high risks of morbidity and mortality in virtue of metastasis and recurrence [15–17]. Therefore, there was a great need and urgency in searching biomarkers of early prognosis and metastasis, and novel treatment targets to improve the survival of cervical cancer. On account of the widespread using of new technologies, many lncRNAs have been proved as a new regulatory player of molecular biology in cervical cancer and other cancers. In this review, we summarized the origin and overview function of lncRNAs, highlighted the roles of lncRNAs in cervical cancer, and outlined the molecular mechanisms of lncRNAs in cervical cancer. Meanwhile, the application of lncRNAs as biomarkers in cervical cancer prognosis and predictors for metastasis was also discussed.

Literature search and selection

Literature search was conducted in PubMed, Embase, Web of Science, ClinicalTrials and the Cochrane Library with the following search terms: “Uterine Cervical Neoplasms,” “Uterine Cervical Neoplasm,” “Cervical Neoplasms,” “Cervical Neoplasm,” “Cervix Neoplasms,” “Cervix Neoplasm,” “Uterine Cervix Cancer,” “Cervical Cancer,” “Uterine Cervical Cancers,” “Uterine Cervical Cancer,” “Cervix Cancers,” “Cervix Cancer,” AND “Long Noncoding RNA,” “lncRNA,” “Long ncRNA,” “Long Non-Coding RNA,” “Long Non Coding RNA,” “Long Non-Protein-Coding RNA,” “Long Non Protein Coding RNA,” “Long Untranslated RNA,” “Long Intergenic Non-Protein Coding RNA,” “Long Intergenic Non Protein Coding RNA,” “LincRNAs,” “LINC RNA”.

Studies were selected when they were satisfied with all the criteria as following: (1) written in English, (2) original articles, (3) focused on the functions and/or mechanism of lncRNAs in cervical cancer. Studies were excluded if (1) meta-analysis, letters, comments, case reports, and reviews and (2) duplicate publications. Totaling 91 papers were identified by the systematic literature search of which 30 duplicates were removed, resulting in 61 papers. Also, 40 articles were removed in view of relevance and types through the title, abstract and full-text screening. Ultimately, 21 papers were included in the relations of lncRNAs with cervical cancer.

Origin of lncRNAs

LncRNAs are prevalent and pervasive in eucaryote, which were considered as anomalies or noises until recently [18]. In recent years, with the emergence of sequencing technique, widespread existence of lncRNAs in eukaryotic organisms has been confirmed as well as their action mechanisms and important biological functions have gradually been elucidated. However, it was not quite clear for the origin of lncRNAs. Ponting et al. put forth several possible approaches for the origination of lncRNAs, such as gene mutations, chromatin’s rearrangement, retrotransposition, tandem duplication events, and insertion of a transposable element [19]. Based on their genomic proximity between neighboring transcripts, the synthesis of lncRNAs can be classified as five ways: (1) sense

strand was synthesized, (2) antisense strand was synthesized, (3) bidirectional synthesis, (4) intronic synthesis, or (5) intergenic synthesis (also known as lincRNAs) [20–22].

Overview function of lncRNAs

To date, an overwhelming majority of lncRNAs have not been well-characterized. However, lncRNAs have been displayed to be drawn into almost every facets of gene regulation, containing epigenetic regulation, imprinting, trafficking of nucleus and cytoplasm, transcription, mRNA splicing [22–24]. Thus, lncRNAs were involved in many diverse biological processes, containing cell cycle, cell proliferation, apoptosis, differentiation, etc. [8–10]. It has been accepted broadly that the molecular functions of lncRNAs were subdivided into four archetypes, namely signals, decoys, guides, and scaffolds [25]. (1) As signals, such as *Xist* and *HOTAIR*; (2) as decoys, like *MALAT1*; (3) as guides; (4) as scaffolds, like *HOTAIR* [22, 25, 26].

Dysregulation and roles of lncRNAs in cervical cancer

Prognosis and tumor progression

Cervical cancer was an intricate disease, which involved in numerous elements. Lots of studies demonstrated that lncRNAs could be used for diagnosing and predicting prognosis tumor [27–30]. In comparison with protein-coding RNAs, applying lncRNAs as biomarkers was of advantage since their own expression was a superior indicator of cancer status [31]. Several lncRNAs were found to be aberrantly expressed in cervical cancer.

A prominent example, the *Hox transcript antisense intergenic lncRNA* (*HOTAIR*), a long intergenic ncRNA (lincRNA), has been proven to make critical effect on the most biological process of cancer and would be a potential new target in tumor treatment [32]. Study showed *HOTAIR* was heightened in cervical cancer tissues and correlated with FIGO stage, lymphatic metastasis, size of tumor as well as invasive depth, indicating its involvement in cervical cancer progression and could be a potential target for diagnosis as well as an independent predictor for overall survival [33]. Meanwhile, elevated *HOTAIR* was markedly associated with tumor recurrence and short overall survival, suggesting circulating *HOTAIR* was commonly upregulated and was a potent prognostic biomarker in cervical cancer [34]. Furthermore, *HOTAIR* might accelerate neoplasm aggressiveness by the upregulation of *VEGF*, *MMP-9*, and epithelial-mesenchymal transition (EMT)-related genes via decreasing the expression of *E-cadherin* while increasing the expression of *β-catenin*, *Vimentin* (*VIM*), *Snail*, and *Twist* [35]. These studies indicated that *HOTAIR* had potential to serve as a new marker for monitoring recurrence and calculating prognosis, also provided an attractive target for targeted therapy in cervical cancer (Fig. 1a).

On the contrary were three downregulated lncRNAs, namely *growth arrest-specific transcript 5* (*GAS5*), *TUSC8*, and *lncRNA low expression in tumor* (*lncRNA-LET*). *GAS5*, a tumor-suppressor lncRNA, was originally isolated from NIH 3T3 cells using subtraction hybridization and encoded at 1q25 [36, 37]. *GAS5* was downregulated in cervical cancer tissues, significantly correlated to advanced cancer progression, and identified as a separate biomarker for forecasting the clinical states of patients in cervical cancer [38]. Vitro assays suggested that knock-downing *GAS5* promoted cell proliferation, migration, and invasion [38]. These results suggested that *GAS5* was a promising marker for cervical cancer in future (Fig. 1d). For another, the *lncRNA XLOC_010588* was also named *tumor suppressor candidate 8* (*TUSC8*), located in 13q14.11, and belonged to lincRNA. The expression of *TUSC8* was dramatically lowered in cervical cancer and linked to FIGO stage, size of tumor, and squamous cell carcinoma antigen [39]. Furthermore, it functioned pivotally in cell proliferation through downregulating *c-Myc* level in cervical cancer [39]. It implicated that *TUSC8* could predict independently overall survival of cervical cancer (Fig. 1c). *LncRNA LET*, a newly identified lncRNA, was found to be downregulated in hepatocellular carcinomas [40], colorectal cancers [40], squamous cell lung carcinomas [40], and cervical cancer [41]. Decreased *lncRNA LET* expression was markedly associated with FIGO stage, lymphatic metastasis, and invasive depth in cervix; meanwhile, compared with cervical cancer patients with higher *lncRNA LET* expression, those with lower *lncRNA LET* owned dramatically worse overall survival [41], suggesting that *lncRNA LET* has the potential to act as a prognosis marker and treatment target of cervical cancer (Fig. 1b).

Invasion and metastasis

It is common knowledge that invasion and metastasis were a root in poor clinical outcome and high relapse rate of cancer patients [42], which part related to some characteristics of cancer cell. LncRNAs have been displayed to be associated with indispensable growth-enhancing capacities and their deregulation contributed to the survival of cancer cell. As a central constituent of *PCR2*, *enhancer of zeste homolog 2* (*EZH2*) was a key histone-modifying enzyme that functioned crucially in the catalysis of *H3K27me3*, leading to transcription silence of target genes [43]. It was reported that *EZH2* expression was increased in neoplasm tissues and displayed as a core point with high-degree centrality [44, 45]. Sun discovered a new lncRNA that was termed *EZH2-binding lncRNA in cervical cancer* (*lncRNA-EBIC*), can enhance cell invasiveness by correlation to *EZH2*, and subsequently downregulating *E-cadherin* level in cervical cancer [46], indicating that

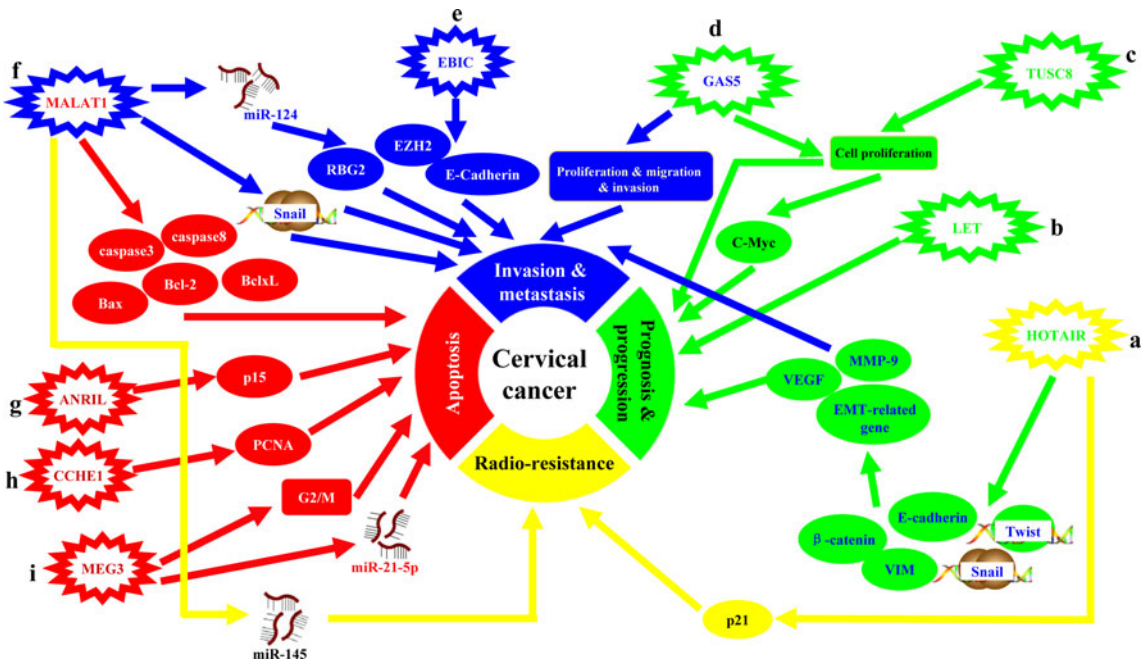

Fig. 1 Dysregulation and functional roles of lncRNAs in cervical cancer. **a** *HOTAIR* could induce radio-resistance via inhibiting *p21* in HeLa cells; increased cell migration and invasion and predicted recurrence and prognosis via regulating the expression of *VEGF*, *MMP-9* and EMT-related genes through the regulation of *β-catenin*, *VIM*, *Snail* and *Twist*. **b** *LncRNA LET* represented a prognostic marker. **c** *TUSC8* predicted independently for overall survival by cell proliferation via lowering *c-Myc* expression level in cervical cancer. **d** *GAS5* was correlated with advanced tumor progression by promoting cell proliferation, and with vascular invasion and lymph node metastasis through promoting cell motility and invasiveness in cervical cancer. **e** *LncRNA-EBIC* promoted cervical cancer cell invasiveness by relating to *EZH2* and subsequently restraining *E-cadherin* expression. **f** *MALAT1* promoted invasion and metastasis via *MALAT1/miR-124/RBG2* signaling or upregulation of Snail level, was involved in radio-resistance through repressing reciprocally *miR-145*, and was involved in cell apoptosis through influencing the level of *caspase-3*, *caspase-8*, *Bax*, *Bcl-2*, and *Bcl-xL* in cervical cancer. **g** *LncRNA-ANRIL* facilitated cell proliferation of HeLa cells via inhibiting the expression of *p15*. **h** *LncRNA-CCHE1* promoted proliferation of cervical cancer cell by enhancing the level of *PCNA*. **i** *MEG3* inhibited cell growth via inducing G2/M cell cycle arrest and cell apoptosis in cervical cancer as well as enhanced cell apoptosis via lowering the *miR-21-5p* content in cervical cancer cells

lncRNA-EBIC may serve as a enhancer in recruitment of *EZH2* to target genes (Fig. 1e).

Another typical example was *metastasis-associated lung adenocarcinoma transcript 1* (*MALAT1*), also called *nuclear-enriched transcript 2* (*NEAT2*), which was found as a prognosis biomarker for the metastasis in lung cancer and even associated with some other solid tumors [47]. It was an interesting target for anti-metastatic therapy in cancer. Our laboratory has declared that descending *MALAT1* level reduced cell migration ability and lessened the tumor growth of cervical cancer in vivo, indicating that *MALAT1* was related to the metastasis process in cervical cancer [48]. Meanwhile, *MALAT1* expression was memorably increased in tumorous tissue in comparison with adjacent tissue and was associated with the size, FIGO stage, vessel invasion, and lymphatic diffusion acting independently as a predictive factor on prognosis in cervical cancer [49]. *MALAT1* promoted cellular motility partly via the *MALAT1/miR-124/RBG2* signaling [50]. Also, our laboratory found that *MALAT1* may promote invasion and metastasis by accelerating EMT process via upregulating the expression of *Snail* in cervical cancer (unpublished data) (Fig. 1f).

In addition, aforementioned *GAS5* and *HOTAIR* were also involved in invasiveness and metastasis of cervical cancer cell lines. Increased *HOTAIR* expression was significantly associated with lymphatic metastasis and depth of cervical invasion [33]. Moreover, knockdown of *HOTAIR* could reduce cell motility and invasiveness of cervical cancer in vitro. *HOTAIR* managed the expression of *VEGF*, *MMP-9*, and EMT-related genes, which were vital for cell migration and metastasis [35]. Further functional studies on *VIM*, a key protein involved in EMT as a typical mesenchymal marker, revealed that *HOTAIR* exerted its functions upon motility and invasion of HeLa cells, at least in part, through the regulation of *VIM* expression [51]. Therefore, *HOTAIR* might strengthen tumor invasiveness via upregulating the expression of *VEGF*, *MMP-9*, and EMT-related genes (Fig. 1a). For another, downregulation of *GAS5* was memorably associated with vessel invasiveness and lymphatic metastasis in cervical cancer patients and promoted cell motility and aggressivity in vitro [38]. Briefly,

lncRNAs worked crucially in invasion and metastasis of cervical cancer (Fig. 1d).

Proliferation and apoptosis

Several studies have indicated that the involvement of lncRNAs in cervical cancer were through affecting on the cell proliferation and apoptosis. Recently, it was found that *lncRNA–antisense non-coding RNA in the INK4 locus* (*ANRIL*) facilitated cell proliferation of HeLa cells via inhibiting the expression of *p15* [52]. In addition, *cervical carcinoma high-expressed lncRNA 1* (*lncRNA-CCHE1*) was dramatically upregulated in cervical cancer tissue, which promoted proliferation of cervical cancer cell by enhancing the level of *proliferating cell nuclear antigen* (*PCNA*) [53] (Fig. 1h). These prompted lncRNAs to act as inferior prognostic biomarkers in cervical cancer.

As a maternally expressed imprinted gene, *maternally expressed gene 3* (*MEG3*) was a tumor-suppressor gene situated in chromosome 14q32 [54]. *MEG3* was downregulated in several cancer types, such as epithelial ovarian cancer [55], colorectal cancer [56], and gastric cancer [57]. Qin revealed that *MEG3* was markedly lessened in human cervical cancer tissues in comparison with matched non-neoplastic tissues, also inhibited cell growth via inducing G2/M cell cycle arrest and cell apoptosis in cervical cancer [58]. Meanwhile, Zhang declared that *lncRNA-MEG3* inhibited cell proliferation as well as enhanced cell apoptosis via lowering the *miR-21-5p* content in cervical cancer cells [59]. These findings indicated that *MEG3* was a tumor suppressor and might be a potential target for tumor therapy (Fig. 1i). Furthermore, our laboratory has reported that involvement of *MALAT1* in cell apoptosis was through influencing the expression of *caspase-3*, *caspase-8*, *Bax*, *Bcl-2*, and *Bcl-xL* in cervical cancer, demonstrating that *MALAT1* might be of crucial importance in the biology of cervical cancer [48] (Fig. 1f).

Radio-resistance

LncRNAs have also been reported to function on radio/chemo-resistance by impairing the response via cell cycle arrest, inhibition of apoptosis, and enhancement of DNA damage repair [60, 61]. Here, we described the rapid emerging roles of lncRNAs in cancer radio-resistance and highlighted a prominent example: the lncRNA *HOTAIR*. As mentioned above, the expression of *HOTAIR* was correlated with prognosis and tumor progression. Here, Jing demonstrated that a high level of *HOTAIR* could induce radio-resistance via inhibiting *p21* in HeLa cells, while knockdown of *HOTAIR* upregulated *p21* consequentially increased the radiosensitivity of C33A cells in vitro as well as sensitized cervical cancer to radiotherapy in vivo [62]. It suggested *HOTAIR* induce radiation resistance through suppressing the level of *p21* in cervical cancer cells. Moreover, *MALAT1* expression was showed dramatically elevated in radio-resistant compared with radio-sensitive patients, and it involved in radioresistance of cervical cancer through repressing reciprocally *miR-145* [63]. Those proposed us that targeting lncRNAs (*HOTAIR* and *MALAT1*) might be potent therapeutic options in cervical cancer, especially in those patients who accepted radiotherapy (Fig. 1a, f).

Molecular mechanisms of lncRNAs in cervical cancer

LncRNAs-proteins/mRNAs

Recently, increasing studies in lncRNAs molecular mechanisms and regulatory networks were implicated that lncRNAs were interrelated to tumorigenesis [64]. LncRNAs interacted with the proteins, miRNAs, and mRNAs and were involved in fundamental biological mechanisms, such as gene activating or repressing, imprinting, transcription, and mRNA splicing, all via modulating gene expression [65]. Comprehend lncRNAs how to regulate the process of gene transcriptional and post-transcriptional can expand vastly our knowledge of cervical cancer. Cervical cancer-related lncRNAs have been declared to direct bind to the target proteins or mRNAs to conduct their post-transcription regulation. Reportedly, *lncRNA-EBIC* could be specifically associated with *EZH2* and inhibited *E-cadherin* expression [46]. Besides, lncRNA *HOXA11-AS* was likely to involve in carcinogenesis and development of cervix cancer via regulating the expression of *HOXA11* [66]. In addition, *lncRNA-CCHE1* promoted proliferation by physically associating with *PCNA* mRNA to increase the expression of *PCNA* in cervical cancer [53]. These studies illustrated that lncRNAs were pivotal in cervical cancer by interacting with mRNAs or proteins.

LncRNAs-miRNAs

Competing endogenous RNA (ceRNA) hypothesis was about RNAs (containing mRNAs, pseudogenes, lncRNAs, and circRNAs) “talk" to each other by miRNA response elements (MREs) as letters of a new language, which can bind competitively miRNAs [67, 68]. That is to say, lncRNAs may function as ceRNA in managing the activities and biological functions of miRNAs, which acted as "miRNA sponges,” shared generally MREs with the transcripts of multiple vital genes and inhibited normal miRNAs targeting vitality on mRNAs [69–71]. Recently, it was reported that *lncRNA-MEG3* served as a cancer suppressor via lessening the expression of *miR-21-5p* in cervical cancer in vitro [59]. One side, *MALAT1* increased cell colony formation and cell cycle regulation while suppressed cell apoptosis through sponging *miR-145* in cervical cancer [63]. For another, *MALAT1* accelerated proliferation and invasion partly via the *MALAT1/miR-124/RBG2*

signaling [50]. These findings could furnish certain evidence on the lncRNA-miRNA interaction in carcinogenesis of cervical cancer.

HPV protein

Human papillomavirus (HPV) infection is the leading reason of cervical cancer and an vital etiologic element in developing cervical cancer [72, 73], which are associated with more than 20 HPV types, and most prevalent HPV type found is HPV type 16 and 18 [74, 75]. However, 80 % of women were likely to be infected with HPV in her life, with only 3 % cervical cancer patients existed in these HPV positive women in their subsequent 20–50 years [76]. Meanwhile, studies have shown that HPV virus alone is not enough to develop cancer [77, 78]. These findings suggested that HPV protein was a prerequisite but not the sole cause, and other molecules may interact with HPV protein. In recent years, a great deal of research showed that ncRNAs, such as lncRNAs and miRNAs, played a vital role in the progression of cervical cancer. Sharma reported the crosstalk between *HPV16 E7* oncoprotein and *lncRNA-HOTAIR* was concomitant with cellular proliferation and metastasis in cervical cancer [79]. Thus, an intimate relationship may exist between HPV protein and lncRNA in cervical cancer.

Furthermore, lncRNAs usually functioned in cervical cancer through a ceRNA mechanism via competing miRNAs. Mounting evidences suggested that miRNAs-HPV protein functioned importantly in cervical cancer. *HPV E6/E7* proteins were a precondition for *miR-135a* as an oncomiR via comparing the oncogenic vitalities of *miR-135a* in HPV E6/E7$^{+/-}$ cell lines, also in NC104-E6/E7 with presence or absence of E6/E7 deletion [80]. Alterations in expression patterns of *miR-146a*, *miR-203*, and *miR-324-5p* were attributed to *HPV16 E5* oncogene that seems to involve in tumorigenesis [73]. Reduction of *miR-218* in human cervical cancer cells was specifically attributed to the HPV16 E6 [81]. Also, underexpression of tumor-suppressive *miR-34a* was ascribed to the expression of oncogenic *HPV 16 E6* [81]. Deregulation of some other miRNAs and their interplay with HPV protein in cervical cancer cell lines has also been studied. These indicated that interactions of HPV protein with miRNAs had done its work in cervical cancer.

RNA m6A methylation of lncRNAs

RNA methylation played an irreplaceable role in biological system, which not only regulated the expression of genes, but also was responsible for regulation of various biological processes. N-Methyladenosine (m6A) was one of the most abundant and ubiquitous internal modification on lncRNAs/mRNAs in higher living organisms [82, 83]. Akin to DNA methylation modification, m6A modification on RNA was reversible, which was formed catalytically by the methyltransferase compound *METTL3/METTL14/WTAP* (Writer) [84] while was responsible for removal by demethylases *FTO* [85] and *ALKBH5* (Eraser) [86] (Fig. 2). One recently developed a method that could determine accurately the m6A status at any site in lncRNAs/mRNAs, termed SCARLET, determined the precise location of the m6A residue and its modification fraction [87]. The authors applied the method to determine the m6A status at several sites in lncRNA *MALAT1* and found that m6A fraction varies between 11 and 77 % in HeLa cell [87]. It suggested that m6A modification of lncRNA *MALAT1* may play a role in cervical cancer. Further research in m6A modification may provide a new horizon into the functional roles of lnRNA in cervical cancer.

Others

Recent years, several studies have showed the epigenetic modifications of lncRNAs, containing DNA methylation, histone modifications (including histone acetylation and methylation), and chromatin structure/remodeling [88–90]. However, rare studies have examined these epigenetic regulations of lncRNAs in cervical cancer. Furthermore, it was reported that lncRNA *MALAT1* could modulate alternative splicing of mRNA by regulating SR splicing factor phosphorylation [91]. In short, lncRNAs can come into play through a variety of mechanisms in cervical cancer (Table 1).

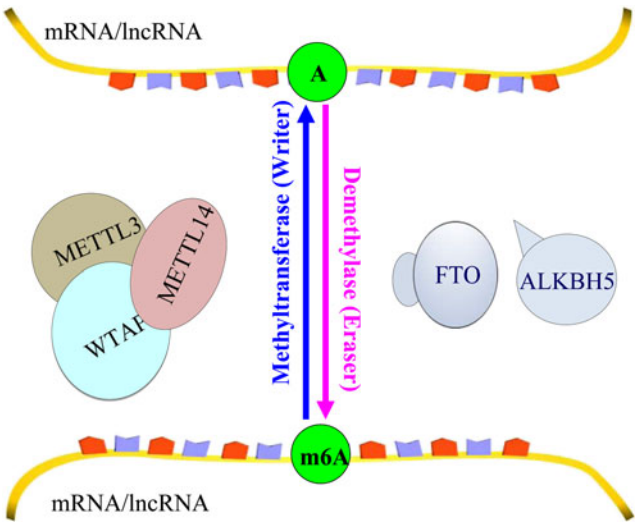

Fig. 2 A schematic diagram of the RNA m6A methylation cycle. N-Methyladenosine (m6A) modification on RNA was reversible. It formed catalytically by the methyltransferase compound *METTL3/METTL14/WTAP* (Writer), while was responsible for removal by demethylases *FTO* and *ALKBH5* (Eraser)

Table 1 LncRNAs are associated with cervical cancer

LncRNA	Dys-regulation	Biological functions in cervical cancer	Molecular mechanism	Reference
GAS5	Down	Predict the clinical outcome	Inhibit cell proliferation, migration, and invasion.	[38]
	Down	Promote cell migration and invasion	(for further study)	[38]
HOTAIR	Up	Predict recurrence and prognosis	Upregulate VEGF, MMP-9 and EMT-related genes	[32–35]
	Up	Increase cell migration and invasion	Upregulate VEGF, MMP-9 and EMT-related genes (eg. VIM)	[33–35, 38]
	Up	Induce radio-resistance	Inhibit p21	[62]
lncRNA-ANRIL	Up	Facilitate proliferation	Inhibit p15	[52]
lncRNA-CCHE1	Up	Promote proliferation	Enhance PCNA	[53]
lncRNA-EBIC	Up	Promote tumor cell invasion	Bind to EZH2 and repress E-cadherin	[46]
lncRNA-LET	Down	Predict overall survival and serve as a potential therapeutic target	(for further study)	[43]
MALAT1	Up	Promote motility and invasion	Increase snail expression; or via MALAT1/miR-124/RBG2 signaling	[48, 50]
	Up	Inhibit cell apoptosis	Regulate caspase-3, caspase-8, Bax, Bcl-2, and BclxL	[48]
	Up	Involve in radio-resistance	Repress reciprocally miR-145	[63]
MEG3	Down	Inhibit cell growth	Induce G2/M cell cycle arrest and apoptosis	[58]
	Down	Inhibit proliferation and enhance apoptosis	Lower miR-21-5p content	[59]
TUSC8	Down	Predict overall survival	Inhibit cell proliferation via decreasing c-Myc expression	[39]

GAS5 growth arrest-specific transcript 5, *HOTAIR* Hox transcript antisense intergenic lncRNA, *lncRNA-ANRIL* lncRNA-antisense non-coding RNA in the INK4 locus, *lncRNA-CCHE1* cervical carcinoma high-expressed lncRNA 1, *lncRNA-EBIC* EZH2-binding lncRNA in cervical cancer, *lncRNA-LET* long non-coding RNA low expression in tumor, *MALAT1* metastasis-associated lung adenocarcinoma transcript 1, *MEG3* maternally expressed gene 3, *TUSC8* tumor suppressor candidate 8

Potential clinical application of lncRNAs in cervical cancer

It is well-known that recurrence and metastasis are the maximal obstacles to the therapy of cervical cancer. Therefore, hunting for the available markers of cervical cancer is essential for improving the prognosis. LncRNAs have the potential to be biomarkers of diagnosis and prognosis in cervical cancer. Take *HOTAIR* in prognostic biomarkers as an example, ROC curve analysis displayed that *HOTAIR* expression was a nice candidate to distinguish neoplasm tissues from non-tumorous tissues and the presence or absence of lymph node metastasis (sensitivity 85.1 %, specificity 64.9 %). The areas under the ROC curve (AUC) were 0.803 (95 % CI 0.762–0.839, $p < 0.0001$) and 0.802 (95 % CI 0.742–0.852, $p < 0.0001$), respectively [33] (Table 2). In addition, lncRNAs were usually expressed in a disease, tissue, cell, or development phase-specific manner [21], thus rendering these lncRNAs serve as promising prognostic biomarkers or treatment targets in cervical cancer.

Conclusion and prospective

To summarize, lncRNAs could be used as potential biomarkers for cervical cancer prognosis (*HOTAIR*, *GAS5*, *TUSC8*, and *lncRNA-LET*), invasion and metastasis (*lncRNA-EBIC*, *MALAT1*, *GAS5*, and *HOTAIR*), be involved in cervical cancer via acting on cell apoptosis (*lncRNA-ANRIL*, *lncRNA-CCHE1*, and *MEG3*), and be used as a potential marker for radio-resistance (*MALAT1* and *HOTAIR*) (Table 1). At the same time, the lncRNAs perform functions in mechanisms of interaction with proteins/mRNAs in cervical cancer on the perspective of the current literatures. Furthermore, these lncRNAs have the potential to serve as promising biomarkers for predicting prognosis and relapse, even

Table 2 Application index of lncRNA in cervical cancer

LncRNA	Function	AUR	Sensitivity	Specificity	Reference
HOTAIR	discriminate tumor tissues from non-tumorous tissues	0.803	60.6 %	87.2 %	[33]
	discriminate presence or absence of lymph node metastasis	0.802	85.1 %	64.9 %	[33]

novel attractive targets for clinical therapy of cervical cancer. However, the exact molecular mechanisms of lncRNAs in cervical cancer remain unclear, further exploration and validation studies are required for elucidating these complicated mechanisms (especially in epigenetic modification of lncRNAs) and the clinical applications of lncRNAs in cervical cancer.

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Compliance with ethical standards

Conflicts of interest None.

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