Long non-coding RNAs on the stage of cervical cancer (Review)

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Abstract. Cervical cancer is one of most malignant gynecological tumors. However, effective means for diagnosing and treating cervical cancer have yet to be identified. A few decades ago, long non-coding RNAs (lncRNAs) were regarded as useless parts of the genome, however, increasing data have demonstrated the importance of lncRNAs in the diagnosis and treatment of cervical cancers. The aim of the present study is to summarize the role(s) of HOTAIR, MALAT1, CCAT2, SPRY4-IT1, RSU1P2, CCHE1, lncRNA-EBIC and PVT1. Approximately 14 lncRNAs are involved in cervical cancer and several important proteins, miRNAs and other molecules and play crucial roles in a few traditional signaling pathways that have been proven to be related to those lncRNAs. In conclusion, lncRNAs may be useful as exact treatment targets and diagnostic biomarkers for improving therapies in cervical cancer patients and lncRNAs may contribute to effective diagnosis and treatment methods for cervical cancer.

Contents

1. Introduction

Long non-coding RNA (lncRNA) is a type of non-coding RNA (ncRNA) that is comprised of over 200 nucleotides (nt) and lacks an open reading region and the capacity for protein coding (1). More than 70% of the human genome has been transcribed into ncRNAs (2). In addition to lncRNAs, other ncRNAs have been identified, such as microRNAs (miRNA), which are small interfering RNAs (siRNA) made up of 20-24 nucleotides. miRNA was the first ncRNA found, though recently lncRNA has garnered more attention. It has been demonstrated that lncRNAs play crucial roles by influencing and changing cell growth, survival, cell cycle, differentiation and apoptosis; they also play a vital part in many diseases, including cancer (3). However, despite the above findings, the biological functions and molecular mechanisms of lncRNAs remain largely unknown (4). Utilizing next generation sequencing (NGS), three generations of sequencing, RNA-Seq, RIP-Seq and RNA array, the biological functions of lncRNAs could be gradually discovered (5), which would be indispensable for optimizing diagnostic and treatment methods for cervical cancer patients.

Cervical cancer is one of the most serious cancers. Each year, there are approximately 500,000 newly diagnosed cases, and 200,000 deaths due to cervical cancer occur worldwide (6). Without appropriate early diagnostic methods, particularly in developing areas, cervical cancer has developed into invasive cancers in a large number of patients, which has led to lower survival rates (7). Traditional radiotherapy and chemotherapy are still the most common therapies for the treatment of advanced cervical cancer; however, these methods are not always effective and can cause severe side-effects (8,9). Therefore, it is urgent that biomarkers and novel treatment targets are found for effective diagnosis and treatment of cervical cancer. Many lncRNAs have been shown to be molecular regulatory factors in cancer and may provide therapeutic targets for improving survival in cases of cervical cancer. In this review, these aspects are explored: the interaction between lncRNAs and miRNA, and the molecular mechanisms involved; the interactions among the proteins (or the mRNAs encoding these proteins at the protein or transcriptome levels). In addition, an overview of research done on the function of lncRNAs in cervical cancer is provided along with prospective clinical applications of lncRNAs in cervical cancer.

2. Modes of interaction between lncRNAs and molecules

Studies of lncRNA molecular mechanisms have shown that lncRNAs are related to tumorigenesis (10). lncRNAs interact

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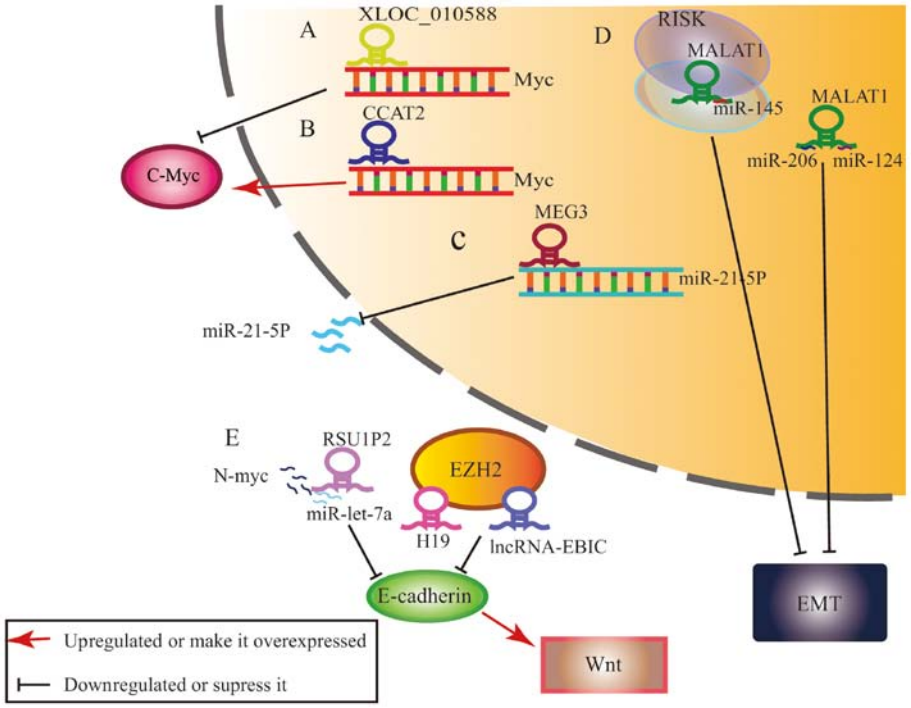

Figure 1. Interaction modes between lncRNAs and molecules. A, XLOC_010588 can suppress C-Myc expression. B, CCAT2 upregulates C-Myc. C-Myc is an oncoprotein that is upregulated in cervical cancer. C, MEG3 downregulates miR-21-5p, which inhibits the biological behavior of cervical cancer. D, MALAT1 sponges miR-124, miR-145 and miR-375 to promote malignant behavior of cervical cancer by inhibition of EMT (epithelial mesenchymal transition). It has been proven that MALAT1 and miR-145 are in the RISC complex. E, Three lncRNAs (lncRNA-EBIC, H19 and RSU1P2) can lower E-cadherin expression, which upregulates the downstream factor, Wnt. lncRNA-EBIC and H19 combined with EZH2. N-myc and miR-let-7a combine with RSU1P2 competitively, RSU1P2 behaves as a ceRNA and thus decreases the amount of miR-let-7a.

with proteins, miRNAs and mRNAs, developing complex mechanistic networks during tumor growth (11). Therefore, clarifying how lncRNAs regulate the process of gene transcription and post-transcription can lead to a better understanding of the pathogenesis of cervical cancer.

lncRNAs-proteins/mRNAs. Cervical cancer-related lncRNAs have been demonstrated to directly bind to target proteins or mRNAs to conduct post-transcriptional modification. Reportedly, lncRNA HOXA11-AS is involved in carcinogenesis through regulating the expression of HOXA11 (12). Besides, lncRNA-TI17313 was named lncRNA-EBIC, due to the fact that it is an EZH2-binding lncRNA in cervical cancer (13). EZH2 is an important member of PRC2, which is involved in several important regulatory mechanisms in cancer. Besides lncRNA-EBIC other lncRNAs, such as HOTAIR, lncRNA-HEIH PVT1 and H19 have been shown to bind to EZH2 and take part in cancer epigenome modulation (14-17). Tseng *et al* (18) shows gain of PVT1 long non-coding RNA expression was required for high MYC protein levels in 8q24-amplified human cancer cells. PVT1 RNA and MYC protein expression correlated in primary human tumours, and copy number of PVT1 was co-increased in >98% of MYC-copy-increase cancers. C-Myc is an oncoprotein, which is upregulated in cervical cancer (19,20). C-Myc acts as a downstream effector of XLOC_010588, CCAT2 and RSU1P2 (21-23) and can also bind and stabilize the Myc via inhibiting its phosphorylation at threonine 58 (24). E-cadherin expression is repressed in cancer and has been found to be upregulated by MALAT1, but repressed by lncRNA-EBIC (25). In addition, lncRNA-CCHE1 increases the expression of PCNA in cervical cancer by associating with PCNA mRNA (26). These studies illustrate that lncRNAs play a role in cervical cancer by interacting with mRNAs and/or proteins.

lncRNAs-miRNAs/circRNA. Since the function of competing endogenous RNA (ceRNA) was discovered, lncRNAs have been regarded as one of the most striking ceRNA and 'talk' to mRNAs or transcribed pseudogenes using microRNA response elements (MREs) as letters (27). lncRNAs work as 'miRNA sponges', which inhibit normal miRNAs targeting vitality on mRNAs (28-30). It has been reported that MEG3 acts as a cancer suppressor via lessening the expression of miR-21-5p in cervical cancer, *in vitro* (31). MALAT1 sponges miR-124, miR-145 and miR-375 promote the malignant behavior of cervical cancer (32-34). In other cancers, H19 has been shown to react with miR-675, miR-140 and miR-200, sponges circRNA MYLK and binds competitively with miRNA-29a-3p to suppress cervical cancer (35-38). These findings demonstrate the interactions between lncRNAs, miRNAs and circRNAs in cervical cancer.

lncRNA-HPV. Human papillomavirus (HPV) infection is a critical factor in the development of cervical cancer (39,40) and highest risk of developing cervical cancer come from HPV type 16 and 18 (41,42). Moreover, some studies have suggested that lncRNAs and miRNAs play significant roles in the progression of cervical cancer by sponging the miRNAs combined with HPV proteins. Other studies have shown evidence of crosstalk between the HPV16 E7 oncoprotein

and lncRNA, such as HOTAIR (43). Increasing evidence suggests that miRNAs-HPV protein like miR-135a-E6/E7 has an important function in cervical cancer (44). Because of the significance of HPV proteins in cervical cancer oncogenicity, finding effective lncRNAs that inhibit HPV protein transcription and translation is necessary (Fig. 1).

3. Functional lncRNAs involved in cervical cancer

HOTAIR. HOTAIR is one of most well-studied lncRNAs in cervical cancer. It is 2.2 kb expressed from the HOXC cluster located in chromosome 12q13.3 (45). In patients with invasive FIGO stage IA-IVB cervical cancer, it was found to be an independent prognostic factor for reduced survival. Furthermore, higher HOTAIR levels have been observed in malignant tissue compared with normal cervix tissue (46,47). A case-control study, including 510 cervical cancer patients (cases) and 713 none-cancer individuals (controls), further indicated that the rs920778T allele conferred elevated HOTAIR transcriptional activity, thus, increasing the risk of developing cervical cancer (48). In addition, rs2366152C was significantly over-represented and affected HOTAIR expression in HPV16-positive cervical cancer cases (49). Another study demonstrated that HOTAIR and HPV16 E7 (oncoprotein HPV E7 is the major transforming agent, which leads to carcinogenesis) strongly interact with each other, but not through the PRC2-complex (a complex that is related to a large number of lncRNAs) (43). The mammalian target of rapamycin (mTOR) has emerged as an important effector in cell-signaling pathways (50). Zhang *et al* (51), found that HOTAIR overexpression upregulates the mTOR pathway in cervical carcinoma cells. A higher level of HOTAIR was detected in the serum from cervical patients compared to normal women, indicating that HOTAIR may be a useful new circulating biomarker in serum. The study also showed that HOTAIR overexpression promoted cervical cancer cell growth, invasion and migration and that HOTAIR knockdown increased cell apoptosis, via the epithelial-mesenchymal transition (EMT) and Notch signaling pathways (52). In a study by Kim *et al* (46), HOTAIR overexpression in SiHa cells and cervical cancer tissue promoted VEGF and mmP-9 protein expression. VEGF and mmP-9 not only play critical roles in the malignant behavior of cervical cancer, but knockdown of HOTAIR upregulates p21 and increases the radio-sensitivity of HeLa cells (53). Many other studies have found that HOTAIR was able to silence some tumor suppressors, such as HOXD10, PTEN and RBM38 and activate some significant signaling pathways, like STAT3, wnt/β-catenin and PI3K/AKT (54-58).

H19. H19 is involved in many kinds of cancer, including ovarian, lung cancer and hepatocellular carcinoma. In spite of this, fewer studies have been done examining the relationship between H19 and cervical cancer than in investigating the relationship between HOTAIR and cervical cancer. Under normal conditions, only fetal tissue and adult muscle express H19, thus it often functions as ncRNA (59). H19 is upregulated in various human cancers, including bladder and breast cancer, and in lung carcinoma cells suggesting an oncogenic function (60). Conversely, in hepatocellular carcinoma, H19-mediated metastasis is suppressed by epigenetic activation of miR-200 suggesting that H19 may function to suppress cancer (35,61,62). In ovarian cancer, H19 upregulates SLUG expression via miR-675, suppressing E-cadherin and activating EMT (36). Kim *et al* (63), explained that in cervical cancer, H19 and IGF2 are expressed abnormally and that this abnormal expression might be associated with the progression of cervical cancer.

XLOC_010588. XLOC_010588 is a 1950nt lncRNA, which has thus far been described in only one publication. It is located in chr13 on the downstream side of TGFβ-stimulated clone-22 (TSC-22). Studies have found that TSC-22 has DNA binding sites and acts as a tumor suppressor. It inferred that XLOC_010588 may suppress the invasive behavior of cancer as well. They found that XLOC_010588 expression suppressed the progression of hepatocellular carcinoma, gastric, colon, breast, cervical and ovarian cancer. In addition, they found that XLOC_010588 inhibited the proliferation of cervical cancer cells via downregulating the expression of oncoprotein c-Myc (21).

MALAT1. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) was first mentioned in association with lung cancer, but has now been found to be largely expressed in most cancers, working as a decoy for splicing factors leading to splicing malfunctioning (64). It has been demonstrated that there is a reciprocal regulation between miR-375 and MALAT1 through suppression of the EMT pathway. MALAT1 also acts as an miR-206 sponge (34). It has also been shown that downregulating MALAT1 in CaSki, HeLa and SiHa cells, as well as in cervical cancer tissues, weakens cancer cell invasion and metastasis by inhibiting EMT and regulation of the MALAT1-miR-124-RBG2 axis (25,33). MALAT1 expression is an independent prognostic factor in addition to tumor size, FIGO stage and lymph node metastasis (65). In radiotherapy to treat cervical cancer, MALAT1 may result in radioresistance by working as a miR-145 sponge (32).

CCAT2. CCAT2 has been shown to be overexpressed in breast cancer and high levels of CCAT2 indicate poor prognosis and CMF adjuvant chemoresistance (66). CCAT2 has also been found to be upregulated in cervical cancer cells and tissues. In HeLa, CaSki and SiHa cervical cancer cells, CCAT2 knockdown inhibits cervical cancer cell proliferation at the G1 phase and triggers cell apoptosis (22,67). However, high CCAT2 expression is indicative of a more advanced FIGO stage, lymph node metastasis and deep cervical invasion and lower survival (68).

SPRY4-IT1. SPRY4-IT1 is an unspliced, polyadenylated 687nt4 transcript derived from the second intron of the SPRY4 gene. Its potential for carcinogenesis was first (69,70) found in melanoma and high levels of SPRY4-IT1 have since been confirmed in gastric, non-small cell lung cancer (NSCLC), esophageal squamous cell carcinoma (ESCC) and other cancers (71-76). Cao *et al* (77), showed that SPRY4-IT1 expression is a good candidate marker for discriminating between tumor tissue and normal tissue and for predicting poor prognoses in patients with cervical cancer.

GAS5. GAS5 has been frequently reported in non-small cell lung cancer (78). GAS5 contributes to the proliferation and apoptosis of lung cancer cells and is indicative of poor prognoses in lung cancer patients. Furthermore, Liang *et al* (79), found lower levels of GAS5 in the plasma of patients with non-small cell lung cancer compared with healthy controls and, based on these results, suggested that GAS5 may represent a novel prognostic indicator and a target for gene therapy in non-small cell lung cancer. In gastric cancer cells, downregulation of GAS5 affects adriamycin sensitivity by promoting hypermethylation (80). It has been demonstrated that downregulation of GAS5 expression in human cervical cancer tissue is associated with poor prognoses in patients. It has also been reported that iRNA-mediated knockdown of GAS5 significantly increases proliferation, migration and invasion capability of cervical cancer cells compared with control cells, which suggests that GAS5 affects the tumorigenesis and progression of cervical cancer (81).

RSU1P2. Ras suppressor protein 1 pseudogene 2 (RSU1P2) upregulation promotes the malignant phenotype of cervical cancer. It was revealed that RSU1P2 acts as a ceRNA of miRNA let-7a and regulates IGF1R and N-myc expression. The transcription factor, N-myc forms a positive feedback loop with RSU1P2, in turn activating its expression (23). To the best of our knowledge, the N-myc positive feedback loop has not been reported in studies of other types of cancer and requires further research.

CCHE1. CCHE1 is located in an intergenic region on chromatin 10. It physically binds to proliferating cell nuclear antigen (PCNA) mRNA and upregulates PCNA expression, which promotes the proliferation of cervical cancer cells. In contrast, decreasing the CCHE1 level via RNA pull-down assays inhibits the proliferation of cervical cancer cells. The present review also report that higher CCHE1 expression was significantly associated with large tumor size, advanced FIGO stage, invasion and low survival (26). There is a similar phenomenon, which occurs in hepatocellular carcinoma. Peng *et al* (82), further confirmed that CCHE1 knockdown inactivates the ERK/MAPK pathway, arresting growth and promoting cell apoptosis.

PAX8-AS1. PAX8-AS1 PAX8 antisense RNA 1 (PAX8-AS1), an important regulator in the upstream region of PAX8 (on chromosome 2q13) (83). PAX8-AS1 contains specific single nucleotide polymorphisms (SNPs), which can represent expression quantitative trait loci (eQTLs) for PAX8. Two eQTLs SNPs (rs4848320 and rs1110839) in PAX8-AS1 decrease the risk of cervical cancer. In addition, PAX8 expression has been recognized as a novel biomarker for fallopian tubes and uterus cancer diagnoses (84,85).

MEG3. The potential function of MEG3 has been studied in a number of cancer types. Downregulation and overexpression of MEG3 alter pituitary tumor cell proliferation, suggesting that MEG3 may be a potential biomarker (86). Likewise, re-expression of MEG3 prevents the proliferation of glioma tumor cells, *in vitro* (87) and in meningioma (88). Expression of MEG3 is lower in cervical cancer tissue compared with non-neoplastic tissue. In human cervical carcinoma cell lines, high levels of MEG3 inhibit cell proliferation, induce G2/M cell cycle arrest and promote apoptosis (89) via regulation of miR-21-5p. Knockdown of MEG3 results in significant upregulation of miR-21-5p expression in HeLa and CaSki cells (31). These results indicate that MEG3 functions as a tumor suppressor, resulting in the inhibition of tumor growth in cervical cancer.

lncRNA-LET. To the best of our knowledge, there has been only one study examining lncRNA-LET. In that study, low levels of lncRNA-LET expression led to significantly poorer overall survival compared to higher lncRNA-LET expression in patients with cervical cancer. Downregulation of lncRNA-LET was associated with a poor prognosis in patients with cervical cancer (90). However, more research is necessary in order to elucidate the lncRNA-LET mechanisms associated with cancer.

lncRNA-EBIC. A recent study reported that one-fifth of all human lncRNAs is physically related to polycomb repressive complex 2 (PRC2, comprised of histone H3 lysine 27 methylase EZH2, SUZ12 and EED), suggesting that lncRNAs may play a general role in leading to transcriptional repression by recruiting polycomb-group proteins to their target genes (91). Several lncRNAs have been shown to physically bind to EZH2, such as lncRNA-HEIH, H19 and HOTAIR, and play important roles in regulating cancer epigenetics (14-16). High levels lncRNA-EBIC and EZH2 promote migration and invasion of cervical cancer cells *in vitro*, resulting in a decrease in E-cadherin expression (13). lncRNA-EBIC has been suggested a key molecule in the migration and invasion of cells and cervical cancer metastasis.

PVT1. Plasmacytoma variant translocation 1 (PVT1) is a highly conserved lncRNA, which is located downstream of MYC (an oncoprotein). PVT1 has attracted great attention due to its frequent co-amplification with MYC in several types of cancer (92-94). In breast and hepatocellular carcinoma, PVT1 function has been attributed to the binding and stabilization of the Myc (18) and Nop2 (95) proteins, respectively. In gastric cancer cells, PVT1 represses the expression of p15 and p16 via co-reaction with EZH2 (14m). Iden *et al* (24), utilized siRNA and LNA-mediated knockdown for detecting the suppressant effects of low PVT1 levels on cervical cancer cell proliferation, migration and invasion, apoptosis and cisplatin resistance. In contrast, high PVT1 levels were correlated with poorer survival. PVT1 also binds directly to EZH2, recruiting EZH2 to the miR-200b promoter and inhibiting miR-200b expression, which also plays an effective role in regulating the behavior of cervical cancer (17) (Table I).

4. lncRNAs may act as circulating tumor biomarkers

It has been demonstrated that many circulating RNAs have diagnostic potential for cancer and are surprisingly stable in blood (96-99). In a study of colorectal cancer, lncRNAs, such as GAS5, HOTAIR, H19 and MEG3 were found in extracellular vesicles (small, phospholipid-enclosed vesicles released by cells into their environment), BCAR4, MEG3 and other

Table I. LncRNAs are related to cervical cancer.

Approved symbol	Approved name	Gene locus	Expression level in patients	Molecules and pathways reacted with lncRNAs in cervical cancer	Refs.
HOTAIR	Hox transcript antisense intergenic RNA	12q13.3	Overexpression	PRC2, LSD1, VEGF, mmP-9, miR-22, miR-34a, Mtor, Notch, Wnt, STAT3, wnt/β-catenin, PI3K/AKT	(46,51,52,54-58)
H19	H19, imprinted maternally expressed transcript	11p.15.5	Downregulation	IGF2	(63)
XLOC_010588	Tumor suppressor candidate 8 (non-protein coding)	13q14.11	Downregulation	c-Myc	(21)
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1	11q13.1	Overexpression	RBG2, E-cadherin, β-catenin, DNMT1, vimentin, ZO-1, miR-124, miR-145, miR-375, EMT	(25,33,34)
CCAT2	Colon cancer associated transcript 2 (non-protein coding)	8q24.21	Overexpression	MYC, miR-17-5p, miR-20a, wnt	(22)
SPRY4-IT1	SPRY4 intronic transcript 1	5q31.3	Overexpression		
GAS5	Growth arrest specific 5 (non-protein coding)	1q25.1	Downregulation		
RSU1P2	Ras suppressor protein 1 pseudogene 2	10q11.21	Overexpression	IGF1R, N-myc, let-7a	(23)
CCHE1	Cervical carcinoma high-expressed lncRNA 1	10q21.1	Overexpression	PCNA	(26)
PAX8 AS1	Paired box8 antisense RNA 1	2q14.1n	Downregulation	TP53, INP1	(84,85)
MEG3	Maternally expressed gene 3	14q32.2	Downregulation	miR-21-5p	(31)
lncRNA-LET	let	chromosome: X	Downregulation		
lncRNA-EBIC	EZH2-binding lncRNA in cervical cancer		Overexpression	EZH2, E-cadherin	(13)
PVT1	Pvt1 oncogene (non-protein coding)	8q24.21	Overexpression	EZH2, Myc, Nop2, p15, p16, miR-200	(17,18,23,95)

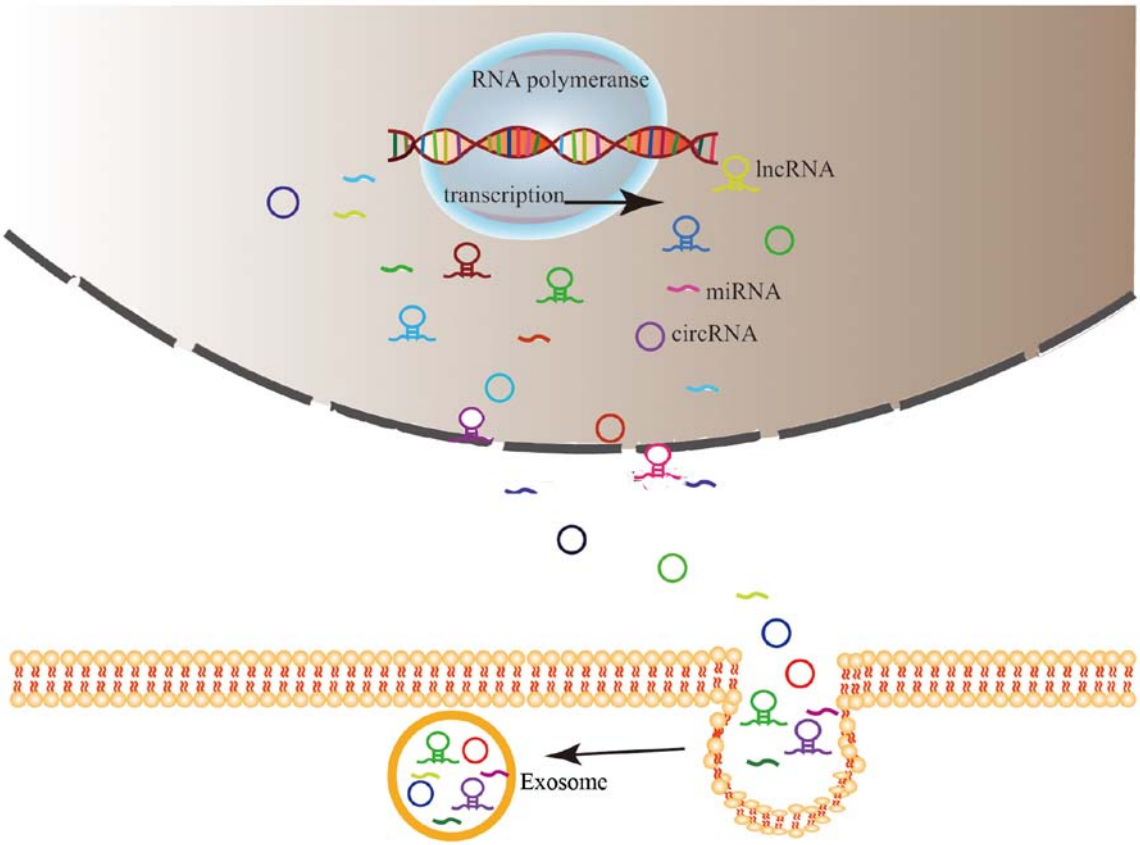

Figure 2. lncRNAs, miRNAs and circRNAs are transcribed in the nucleus and pass through the karyotheca and some go into exosomes. Exosomes with these RNAs play an important role in cervical cancer.

19 lncRNAs were found to be significantly different between the exosomes of samples from healthy people compared to those with colorectal cancer. These have the potential for use as biomarkers for the diagnosis of colorectal cancer (100). In other types of cancer, lncRNAs can be detected in the plasma. PCA3, MALAT-1 and lncRNA-PCAT-18 have been identified as potential biomarkers for patients with metastatic prostate cancer (101-103). It has also been reported that the H19 plasma level was significantly higher, with a sensitivity of 74% and a specificity of 58%, in patients diagnosed with gastric cancer (GC) compared with healthy controls (104,105). In hepatocellular carcinoma patients the levels of the lncRNAs, HULC, LINC00152, RP11-160H22.5, XLOC_014172, LOC149086 and lncRNA-AF085935 are upregulated in the plasma, particularly lncRNA-AF085935, which was found not only in the plasma from cancer patients, but also in patients infected with hepatitis B (106-109). Only one circulating lncRNA, HOTAIR, has been demonstrated in patients with cervical cancer. Li *et al* (110), identified plasma HOTAIR overexpression in the serum of cervical cancer patients. However, the study of circulating lncRNAs is new and there are still several challenges, such as finding better ways to collect good quality plasma/serum from whole-blood, handling lncRNA quantification and cancer-related genes may be expressed highly in cancer tissues, but lower expressed in serum, which must be overcome in order to identify lncRNAs, which can be relied upon as novel, specific and sensitive cancer biomarkers.

Exosomes are identified as important members of circulating tumor biomarkers and can be found in blood, urine and other extracellular fluids (111,112) that contain a large variety of biological components such as proteins, mRNAs, miRNAs and lncRNAs (113). The expression levels of HOTAIR, MALAT1 and MEG3 were significantly different in exosomes isolated from cervical cancer patients compared to those isolated from normal controls (114). Exosomes can also transmit lncARSR, acting as a ceRNA, in renal cancer. The above results indicate that exosome could play a vital role in finding more sensitive and specific circulating tumor biomarkers (Fig. 2).

5. Conclusion and Prospective

Although only a few lncRNAs have been functionally characterized, they play a novel role in the regulation of gene expression. In cervical cancer, lncRNAs are important as potential biomarkers for cervical cancer prognosis, invasion, metastasis, chemo-resistance and radio-resistance. At the same time, the lncRNAs interact with circRNA, miRNA, proteins/mRNAs and can be detected in plasma, serum, exosomes and other vesicles in extracellular fluid, which has opened up new avenues for their use as easily accessible biomarkers. However, the potentially significant regulatory mechanisms of lncRNAs in cervical cancer need further exploration and characterization.

Inhibiting oncogenic lncRNA might be the most direct approach for the treatment of cervical cancer. As yet, no RNA

interference-based drug has been approved; achieving viable and efficient inhibition of lncRNA via siRNAs, miRNAs or by another method, while avoiding side-effects, presents a great challenge and necessitates further study.

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