Apoptosis
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REVIEW

Long non-coding RNAs as critical regulators and novel targets in cervical cancer: current status and future perspectives

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Abstract
Cervical cancer is among the leading causes of cancer-associated mortality in women. In spite of vaccine availability, improved screening procedures, and chemoradiation therapy, cervical cancer remains the most commonly diagnosed cancer in 23 countries and the leading cause of cancer deaths in 36 countries. There is, therefore, a need to come up with novel diagnostic and therapeutic targets. Long non-coding RNAs (lncRNAs) play a remarkable role in genome regulation and contribute significantly to several developmental and disease pathways. The deregulation of lncRNAs is often observed in cancer patients, where they are shown to affect multiple cellular processes, including cell cycle, apoptosis, angiogenesis, and invasion. Many lncRNAs are found to be involved in the pathogenesis as well as progression of cervical cancer and have shown potency to track metastatic events. This review provides an overview of lncRNA mediated regulation of cervical carcinogenesis and highlights their potential as diagnostic and prognostic biomarkers as well as therapeutic targets for cervical cancer. In addition, it also discusses the challenges associated with the clinical implication of lncRNAs in cervical cancer.

Keywords lncRNAs · Clinical biomarkers · Pathogenesis · Therapeutic targets · Cervical cancer

Introduction

Cervical cancer is one of the leading malignancies among women worldwide primarily associated with cervix uteri. It is the most commonly diagnosed female reproductive cancer and the fourth most frequent reason of deaths among females. The increase in mortality rates due to this malignancy is largely because of the delayed diagnosis and untreated status among women. The data from GLOBOCAN database reflects the increased estimates of cervical cancer incidence as well as its mortality. In 2020, the health emergency caused by Covid-19 led to a prolonged shutdown of key medical facilities that resulted in the suspension of screening programs and reduced access to essential

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healthcare facilities. The eventual outcome of the Covid crisis was observed in the form of advanced stage diagnosis and induced mortality of cervical cancer patients at the global level. In the same year, 604,127 new cases (constituting 3.1% of all site cancer incidences) and 341,831 deaths (constituting 3.4% of all site cancer deaths) from cervical cancer were reported according to the global cancer patterns [1]. Among all regions, Sub-Saharan Africa has the highest incidence and mortality rate so far. The variations in incidence rate lie in the development index of nations along with their poverty rates that together account for ~ 50% mortality variance at global level [2]. It is not only the international variations which account for such differences but the disparity also exists within the countries exhibiting high development index [3]. Although this malignancy is largely preventable by using primary and secondary cautions including human papillomavirus (HPV) vaccination and regular screening but the social taboos and their poor implementation renders them insufficient. More than 80% of high-income nations have implemented programs for HPV vaccination as compared to less than 30% of low- and average-income nations due to limited resources [4]. As far as the screening is concerned, only ~ 45% females in low- and average-income nations are ever covered under cervical cancer screening as compared to more than 60% females in high-income nations [5].

The advancement of technology has facilitated the area of diagnosis and treatment of cervical cancer but the lacunae are still there in the form of severe side effects and limited effectiveness of the diagnostic and therapeutic strategies [6, 7]. HPV-DNA testing along with cytological testing has been introduced for efficient screening, but its low specificity limits its application for accurate diagnosis. The treatment for early stage tumor involves surgical removal, radiotherapy and combination of cisplatin-aided chemotherapy along with radiotherapy in case of locally advanced tumor. These treatment regimens for cervical cancer are not without their side effects. Majority of the patients administered with radiotherapy experience bladder irritation, diarrhea and complications associated with small intestine, genitourinary tract and vaginal region. Hematologic as well as gastrointestinal toxicity is reported from concomitant chemo-radiotherapy treatment [8]. Other drugs evaluated for their curative potential in cervical cancer include paclitaxel, bevacizumab, carboplatin, topotecan and gemcitabine. Out of these, paclitaxel/carboplatin and cisplatin/paclitaxel are effective combinations that are often considered for treating cervical cancer patients. However, the patients who develop chemoresistance show poor prognosis and reduced overall survival even with these combinatory treatment strategies. In addition to this, HPV infection is not curative by traditional therapies. Its persistence on the target site results in the recurrence of tumor whenever assisted by other risk factors. For the timely diagnosis and effective treatment, more efficient ways are required to be identified. Thus, identification of new therapeutic candidates is crucial that can probably be achieved with the help of defined molecular targets [9]. Regarding this, some recently explored molecular targets are offering efficient outcomes in trials but are not ready to serve. Till now, there is no specific target drug formulated for cervical cancer treatment. EGFR (epidermal growth factor receptor) antagonist, multi-targeted tyrosine kinase inhibitors, anti-angiogenesis agents and HPV directed therapy are few promising research avenues being widely explored for their efficacy [10]. In this direction, long non-coding RNAs have shown great potential as biomarkers and therapeutic targets [11, 12].

Biogenesis and functions of lncRNA

The human cellular processes are often attributed to the function of proteins but surprisingly only 2% of the human genome actually codes for the proteins. It is even more interesting to note that 70% of the genome is transcribed implying that the majority of the transcripts, referred to as non-coding RNA, do not code for any protein. The non-coding RNAs (ncRNAs) are the key regulatory molecules responsible for smooth functioning of all cellular processes. Among all, the long non-coding RNAs (lncRNAs) comprise of the ncRNAs having a size greater than 200 bp (Fig. 1). Once regarded as useless, lncRNAs are now believed to be the excellent regulators of the genomic activities [13]. lncRNAs can be classified on the basis of their genomic origin (exonic, intronic, intergenic or promoter regions) and their transcriptional direction (sense, antisense and bi-directional). Their biosynthesis in relation with specific physiological conditions and their mechanism of action are still inadequately described in literature. LncRNAs have been widely studied for their role in genomic imprinting, lineage determination, as molecular signals, guide to ribonucleoproteins, as decoy for entrapping regulatory protein and scaffold to recruit vivid effector molecules [14].

To have an understanding of the functional roles of lncRNAs, it is crucial to characterize, locate and annotate them separately in normal developmental processes and malignant conditions. There are clear findings demonstrating that lncRNAs possessing cis- and trans-regulatory functions are the crucial modulators of cellular processes and critical influencers of carcinogenesis. Their tremendous capabilities to modify gene expression at chromatin, transcription as well as post-transcription and epigenetic level distinguish them from other regulatory elements in the genome. The possible molecular mechanisms of lncRNAs

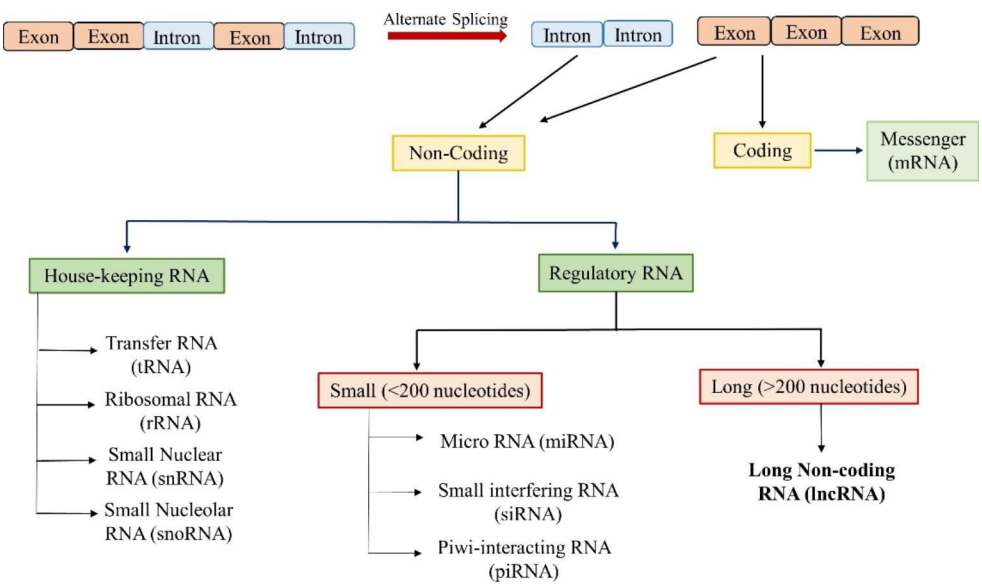

Fig. 1 A schematic representation of different classes of non-coding RNAs

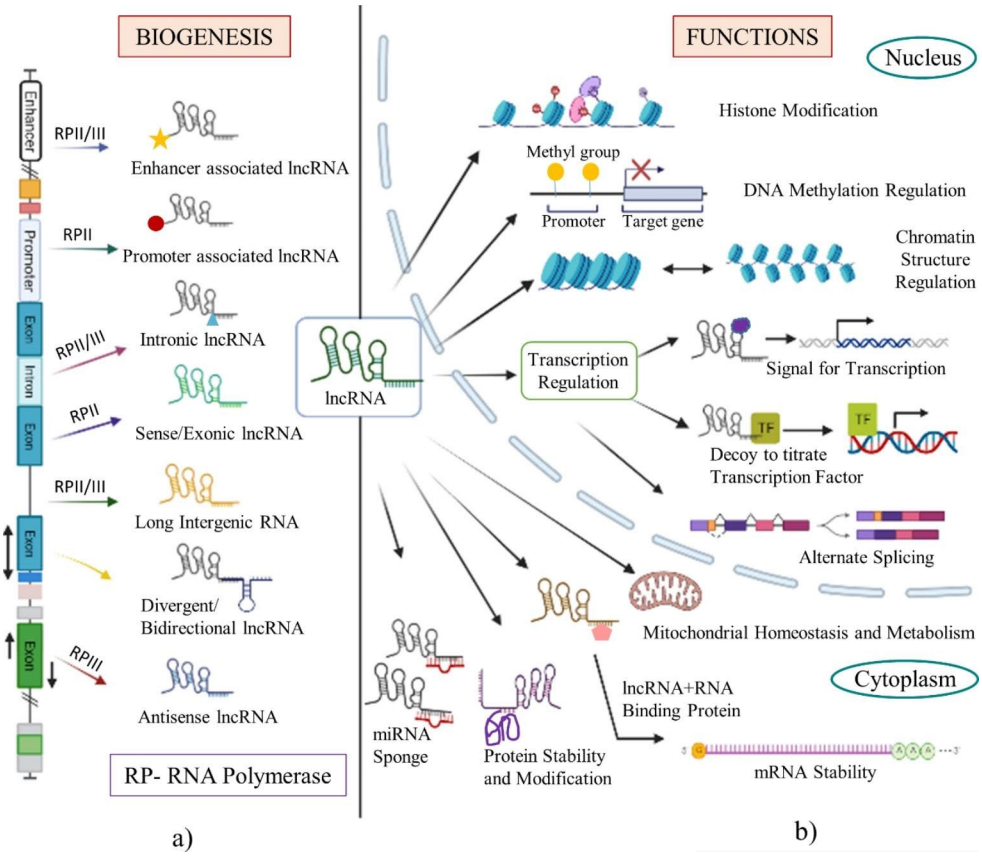

Fig. 2 Illustrative overview of biogenesis and functional mechanisms of lncRNA: (a) Diverse lncRNAs are transcribed from different regions of DNA assisted by RNA Polymerase action and named according to the regions from which they are transcribed. (b) In the nucleus, they regulate both genetic as well as epigenetic phenomena such as chromatin remodeling, DNA methylation, transcriptional activities including its activation, recruitment of transcription factors, and mRNA splicing. They also regulate the post transcriptional events in the cytoplasm through regulation of mRNA and protein stability, mitochondrial metabolism and by acting as ceRNA to miRNA.

involve their interaction with mRNAs, miRNAs, proteins and formation of complex networks during tumorigenesis. The post-transcriptional modification by lncRNAs is carried out via direct binding of lncRNAs, either with the mRNAs or with the proteins. The lncRNAs have also been shown to act as ceRNA (competing endogenous RNA), by using MRE (microRNA response element) and working as miRNA sponge to inhibit their mRNA targets [15] (Fig. 2).

In the past decade, a number of lncRNAs that play essential functions in genome regulations have been identified and documented. The expression of lncRNAs are found to be modulated by transcriptional as well as epigenomic factors and their abnormal expression is observed to be significantly associated with the cancers of different body organs. There seems to be direct correlation of lncRNAs expression with all the major hallmarks of cancer has also been

reported. lncRNA HOTAIR (HOX Antisense Intergenic RNA) is often found to be deregulated in a variety of disorders including cancer of different organs such as breast, lung, pancreas, colon, gall bladder etc. It plays a critical role in chromatin regulation by interacting with epigenetic regulators like LSD1 (Lysine-specific demethylase 1) and PRC2 (Polycomb repressive complex 2). In addition, it could disrupt protein-protein binding by competitively binding to proteins like BRCA1 (Breast cancer gene 1) in breast cancer. It is also reported to behave as ceRNA for miR-130a in gall bladder cancer cells [16]. The lncRNA UCA1 (Urothelial Carcinoma Associated 1) promotes tumor growth by binding with tumor suppressor miRNAs, directing several genetic and epigenetic changes and the activation of different signaling mechanisms [17]. Another oncogenic lncRNA LUCAT1 (Lung cancer related transcript 1) was first discovered in lung cancer of smokers. Thereafter, it has also been found to be deregulated in cancers of other sites including breast, liver, ovary, kidney and thyroid [18]. HOXA-AS2 (HOXA cluster antisense RNA 2) is a cancer-related novel lncRNA that is involved in various bio-processes and different regulatory mechanisms through direct or indirect pathways [19]. The oncogenicity of another lncRNA Small nucleolar RNA host gene 12 (SNHG12) has been observed in osteosarcoma, glioma, breast and gastric cancer. It acts via the sponging of miRNAs to regulate downstream targets [20]. Increasing evidence suggests that the deregulation of many lncRNAs is often observed in tumorigenesis. The genetic changes in lncRNA because of single nucleotide polymorphism, copy number alterations, chromosomal aberrations and epigenetic alterations like DNA methylation can directly contribute to the initiation and progression of tumor. Besides genetic and epigenetic phenomena, the mechanisms involving the recruitment of transcription factors, tumor suppressors and oncogenic signaling, and hypoxia like factors can also modulate the expression of cancer specific lncRNAs [21].

LncRNAs involved in pathogenesis of cervix uteri

A number of lncRNAs are frequently found to be deregulated in cervical cancer patient samples. lncRNAs that have significant roles in pathogenesis of cervical cancer are listed in Table 1 along with their molecular mechanisms. Many of these lncRNAs are among the key causal factors of tumorigenesis and therefore excellent molecular targets for therapy. The lncRNAs have also shown potency to track metastasis events, to evaluate prognosis and recurrence of the disease and to guide personalized therapies. Aberrant patterns of lncRNAs expression are highly evident in cervical cancer and often correlate with FIGO (International Federation of Gynecology and Obstetrics) staging, tumor size and patient survival. In one of the studies on cervical cancer, approximately 22,000 aberrantly expressed lncRNAs were detected using microarray techniques, out of which ~ 11,500 were upregulated and ~ 10,500 were downregulated in cervical cancer [22]. The huge number of cellular lncRNAs and the wide array of their regulatory functions make them important players in cervical cancer. This section discusses the present status of lncRNAs in cervical cancer.

LncRNAs as clinical utility targets

Role in diagnosis and prognosis

The lncRNAs show a highly tissue specific expression which makes them an excellent choice for biomarkers in disease pathologies. They have already been proposed as potential diagnostic and prognostic biomarkers in cancers of different sites including breast, lung, liver, prostate, cervical and pancreas [126–130]. LncRNAs PCA3 (Prostate cancer gene 3) and MALAT-1 (Metastasis associated lung adenocarcinoma transcript 1) show the potential to be used in clinical practices as diagnostic biomarkers for prostate cancer [131, 132]. Interestingly, the lncRNAs possessing diagnostic potential are also found in the body fluids with satisfactory stability, thereby enabling a painless diagnosis for the patient. High HIF1A-AS1 (Hypoxia inducible factor 1 A-antisense RNA 1) level in serum is a novel diagnostic biomarker in colorectal cancer that can also be used as a predictor of worse prognosis [133]. Circulating lncRNAs like AFAP1-AS1 (Actin fiber associated protein 1-antisense RNA1) and MALAT-1 were found to show significantly reduced levels in serum post-therapy in nasopharyngeal carcinoma (NPC). These are represented as serum biomarkers of novel diagnostic and prognostic value in the patients with NPC [134]. In addition to these, PVT1 (Plasmacytoma variant translocation 1), GAS5 (Growth arrest specific transcript 5), H19 are also suggested to be used as biomarkers within bio-fluids in patients of melanoma, breast cancer and non-small cell lung cancer [135–137]. Besides acting as molecular markers of diagnosis as well as prognosis, the expression of lncRNAs can also predict the sensitivity to radio- and chemo-therapy. PVT1 and NEAT1 (Nuclear enriched abundant transcript 1) are two examples of such lncRNAs serving as functional biomarkers in lung cancer [138].

In cervical cancer too, many deregulated lncRNAs are detectable in bodily fluids. HOTAIR is the first investigated circulating lncRNA that was observed to be overexpressed in bodily fluids of cervical cancer patients [139]. The expression of another lncRNA, PVT1 was significantly

Table 1 LncRNAs involved in pathogenesis of cervical cancer

LncRNAs	Properties	Targets	Molecular mechanism	References
Upregulated (ONCOGENES)				
HOTAIR	Proliferation, Apoptosis, Epithelial-Mesenchymal Transformation (EMT), Migration, Invasion, Radio/Chemo-resistance	p21, miR-29b	Inhibition of p21; HIF1-α overexpression; through HOTAIR/miR-29b/PTEN/PI3K signaling axis	[23–25]
PVT1	Proliferation, Migration, Invasion, EMT, Chemo-resistance	miR-140-5p, miR-424, miR-195, miR-503	Causes overexpression of SMAD3 by miR-140-5p sponging; negative regulation of miR-424; inhibition of TGF-β1; via PVT1/miR-195 and miR-503/ARL2 axis	[26–29]
MALAT1	Proliferation, EMT, Migration, Invasion, Radio-resistance	miR-145, miR-429	miR-145 and miR-429 sponging	[30, 31]
UCA1	Proliferation, Apoptosis, Migration, Invasion, Radio/Chemo-resistance	miR-299-3p, miR-204, miR-122-5p	Downregulates p21 and caspase-3; upregulates CDK2 expression; modulation of miR-299-3p and miR-204/KIF20A expression; via miR-122-5p/SOX2 axis	[32–35]
NEAT1	Proliferation, Migration, Invasion, EMT, Radio-resistance	miR-9-5p, miR-133a, miR-193b-3p, miR-124	Via sponging miR-9-5p, regulation of miR-133a/SOX4 axis, miR-193b-3p/CCND1 axis, miR-124/NF-κB	[36–39]
DLX6-AS1	Proliferation, Metastasis	miR-16-5p, miR-199a	Targets miR-16-5p/ARPP19 axis; acts ceRNA for miR-199a	[40, 41]
TUG1	Proliferation, Apoptosis, EMT, Migration, Chemo-resistance	miR-138-5p, miR-381-3p	Modulates miR-138-5p/SIRT1 axis; triggers MAPK pathway; miR-381-3p sponging	[42, 43]
LINC00511	Proliferation, Motility, Apoptosis, Invasion, Chemo-resistance	RXRA, miR-324-5p	Promotes RXRA transcription factor regulated PLD1; ceRNA to regulate miR-324-5p/DRAM1 axis	[44, 45]
DARS-AS1	Proliferation, Apoptosis, Migration, Invasion	miR-628-5p, ATP1B2	Activates notch cascade through miR-628-5p/JAG1 axis; triggers cGMP-PKG pathway	[46, 47]
TDRG1	Proliferation, Migration, Invasion	miR-326, miR-330-5p, miR-214/5p	miR-326 sponging to modulate MAPK1; acts ceRNA of miR-330-5p to increase ELK1 expression; miR-214/5p sponging to modulate SOX4	[48–50]
ANRIL	Proliferation, Migration, Invasion	miR-186	Increases expression of CyclinD1, CDK4, CDK6 and E-cadherin; regulation of G2/M phase and p15; miR-186 sponging; targets PI3K/AKT	[51–53]
CCAT1	Proliferation, Apoptosis, Migration, Invasion, EMT	miR-181a-5p	Modulates miR-181a-5p/MMP14 axis; activates Wnt signaling pathway	[54, 55]
H19	Proliferation, Apoptosis	miR138-5p	Acts as miR138-5p sponge	[56]
CCHE1/CCEPR	Proliferation, Apoptosis	PCNA	Upregulation of PCNA mRNA	[57, 58]
BCYRN1	Proliferation, Apoptosis, Migration	miR-138	Targets miR-138	[59]
BDLNR	Proliferation, Apoptosis, Migration	YBX1	Triggers PIK3CA expression and activates PI3K/AKT cascade through YBX1 binding	[60]
XIST	Proliferation, Apoptosis, EMT, Invasion	miR-200a, miR-140-5p, miR-889-3p	Binds competitively to miR-200a to upregulate Fus; modulates ORC1 and miR-140-5p; targets miR-889-3p/SIX1 axis	[61–63]
XLOC_006390	Proliferation, Migration, Invasion	miR-338-3p, miR-331-3p	Acts ceRNA for miR-338-3p and miR-331-3p; partly regulates SET8	[64, 65]
EBIC	Proliferation, Migration, Invasion	EZH2	Via TAL1/lnc-EBIC/KLHDC7B axis	[66]
XLOC_008466	Proliferation, Apoptosis	miR-216b	miR-216b sponging	[67]
POU3F3	Proliferation, Invasion	miR-127-5p	Regulates miR-127-5p/FOXD1 axis induced by SP1	[68]
CCAT2	Proliferation, Apoptosis, Invasion	-	Enhances MYC expression	[69]
HOXD-AS1	Proliferation, Apoptosis, Migration, Invasion	ELF1, miR-877-3p	Via upregulating FRRS1 and through miR-877-3p/FGF2 axis	[70, 71]
SRA	Proliferation, EMT, Migration, Invasion	-	Via Notch signaling	[72]
RSU1P2	Proliferation, EMT, Migration, Invasion	let-7a	Acts as ceRNA for let-7a	[73]
CASC11	Proliferation, Migration	-	Initiation of Wnt/β-Catenin cascade	[74, 75]

Table 1 (continued)

LncRNAs	Properties	Targets	Molecular mechanism	References
Upregulated (ONCOGENES)				
FAM83H-AS1	Proliferation, Apoptosis, Migration	-	Controlled via E6-p300 pathway	[76]
LUCAT1	Proliferation, Migration, Invasion, EMT	miR-181a	Increased transcription by SP1 sponges miR-181a	[77]
LINC00473	Proliferation	-	Suppresses degradation of ILF2	[78]
CRNDE	Proliferation, Apoptosis, Migration, Invasion	miR-183, miR-4262	miR-183 sponging to induce CCNB1 expression; inhibition of PUMA expression; targets PI3K/AKT; regulates miR-4262/ZEB1 axis	[79–82]
SNHG4	Progression	miR-148a-3p	Increases c-Met expression via miR-148a-3p interaction	[83]
TP73-AS1	Proliferation, Migration	miR-329-3p, miR-607	Competitively bind to miR-329-3p to upregulate ARF1 and downregulate SMAD2; regulation of miR-607/cyclin D2	[84–86]
CTS	Migration, Invasion, EMT, Apoptosis	miR-505	Activates SMAD/TGF cascade by competitive binding with miR-505; targets ZEB2	[87]
ZFAS1	Proliferation, Migration, Invasion, Chemo-resistance	miR-647	Induces chemo-resistance to cisplatin; suppress miR-647 via m^6A modification by METLL3	[88, 89]
NCK1-AS1	Proliferation, Migration, Apoptosis	miR-134-5p, miR-6857	Enhances MSH2 activity; shows competitive binding with miR-134-5p; NCK1-AS1/miR-6857/CDK1 crosstalk	[90, 92]
LINC00958	Proliferation, Metastasis, Radio/Chemo-resistance	miR-5095, miR-625-5p	Modulates expression of RRM2 via miR-5095 competitive binding; through miR-625-5p/LRRC8E axis	[93, 94]
AL592284.1	Proliferation, Metastasis	miR-30a-5p	Via miR-30a-5p/Vimentin/EMT axis	[95]
DLEU2	Proliferation, Migration	p53	Through DLEU2/p53/NOTCH1 axis	[96]
SFTA1P	Proliferation, Migration, invasion	PTBP1	Via SFTA1P/PTBP1/TPM4 axis	[97]
FLVCR1-AS1	Proliferation, Migration, invasion, EMT	miR-23a-5p, miR-381-3p	Via FLVCR1-AS1/ miR-23a-5p /SLC7A11 and FLVCR1-AS1/ miR-381-3p /MAGT1 axis	[98, 99]
HCP5	Proliferation, Migration	miR-216a-5p	Via regulation of HCP5/miR-216a-5p/CDC42	[100]
MAGI2-AS3	Proliferation, Migration, Invasion	miRNA-31-5p	MAGI2-Antisense RNA 3/ miRNA-31-5p axis	[101]
LINC00514	Proliferation, Invasion	miRNA-708-5p	LINC00514/miRNA-708-5p/HOXB3 axis	[102]
LINC01012	Proliferation, Migration	-	Downregulation of CDKN2D	[103]
ABHD11-AS1	Proliferation, Migration, Invasion	-	Downregulation of miR-1254	[104]
KCNQ1OT1	Proliferation, Metastasis	miR-1270	KCNQ1OT1/miR-1270/LOXL2 axis through PI3K/AKT pathway	[105]
HOXA-AS3	Proliferation, Migration, Invasion	-	By sponging of miR-29a-3p	[106]
Downregulated (TUMOR SUPPRESSORS)				
MEG3	Proliferation, Apoptosis, Migration, Invasion	miR-21	miR-21 modulation; regulation of PI3K/AKT/Bcl-2/Bax/p21 and PI3K/AKT/MMP-2/9 signaling axis, hypermethylated promoter; ubiquitin based degradation of p-STAT3 protein	[107–110]
GAS5	Proliferation, Migration, Invasion, Radio/Chemo-resistance	miR-21, miR-196a, miR-205	Modulates PTEN homologues via miR-21 downregulation; controls Akt phosphorylation; regulated by P-STAT3; downregulates miR-196a and miR-205	[111–113]
CASC2	Proliferation, Migration, Radio/Chemo-resistance	miR-21	Downregulates p-AKT; causes overexpression of PTEN via direct inhibition of miR-21	[114, 115]
XLOC_010588	Proliferation	c-Myc	Via c-Myc upregulation	[116]
PTCSC3	Proliferation, Metastasis, Invasion	miR-574-5p	Via miR-574-5p sponging	[117]
ZNF667-AS1	Progression	miR-93-3p	Modulates miR-93-3p dependent PEG3	[118]
MIR503HG	Proliferation, Invasion, Apoptosis	miR-191	Via miR-191/CEBPB axis	[119]
STXBP5-AS1	Proliferation, Invasion	miR-96-5p	Sponging of miR-96-5p	[120]
TUSC8	Migration, Invasion	miR-641	Via miR-641/PTEN axis	[121]
LINC00861	Proliferation, EMT, Migration, Invasion,	miR-513b-5p	miR-513b-5p/PTEN/AKT/mTOR	[122]
RP11-284F21.9	Proliferation, Invasion, Migration	miR-769-3p	Through RP11-284F21.9/miR-769-3p /PPWD1 axis	[123]

Table 1 (continued)

LncRNAs	Properties	Targets	Molecular mechanism	References
Upregulated (ONCOGENES)				
DGCR5	Proliferation, Invasion, Migration	-	Via targeting Wnt signaling	[124]
ALOX12-AS1	Proliferation	miR-3171	Interaction with AGO2 and miR-3171 sponging	[125]

high in cervical cancer patients and its elevated expression was found to be related with poor overall survival. Moreover, it was stably detected in bio-fluids of cervical cancer patients indicating that PVT1 may serve as a non-invasive biomarker [140]. LncRNA MEG3 (Maternally expressed gene 3) is known for its tumor suppressor activities in cervical cancer. In a study conducted by Zhang et al. (2017), MEG3 was downregulated due to hypermethylation of its promoter region in cervical cancer tissue as well as plasma of the patients. MEG3 methylation level in the plasma was high enough to predict lymph node metastasis, high risk-HPV (hr-HPV) infection along with overall and recurrence free survival thus showing its potential as plasma based biomarker [141]. Also, the expression of MEG3 was relatively low in patients with metastasis and stage III/IV as compared to the non-metastatic and stage I/II patients [142].

Significant correlation of different lncRNAs has also been observed in cervical cancer with respect to the FIGO staging, tumor size, histological grade and lymph node metastasis. The expression of ZFAS1 (Zinc finger protein X-linked antisense 1) was found to be statistically associated with histological grade, stage of tumor, lymph node metastasis as well as the myometrial invasion depth ($p < 0.05$) in cervical cancer patients [88]. A close association of LINC00511 (Long intergenic non-protein coding RNA 511) expression level was found with the tumor size, staging and lymph node metastasis ($p < 0.05$) as revealed by the clinicopathological data [143]. The expression of another lncRNA MIR503HG (MIR503 host gene) was found downregulated in both HeLa cell line and cancer tissues as compared to the adjacent normal tissues. The downregulation of MIR503HG was observed to be associated with TNM stage, tumor size and metastasis to the lymph node [119]. Highly expressed lncRNA DLEU2 (Deleted in leukemia 2) was also shown to closely correlate with the topography of tumor except the lymph node stage and metastasis in cervical cancer cases [96]. A positive correlation of the expression level of BLACAT1 (Bladder cancer-associated transcript 1) was demonstrated with the FIGO staging, histological grade and distant metastasis [144]. However, in another study conducted by Cheng et al. (2020), no significant difference was reported in the expression of BLACAT1 among the clinical stages [145]. The contradictory results could perhaps be attributed to the heterogeneity among the patient samples used for the studies. This, however, needs to be proven experimentally. The lncRNAs which exhibit direct correlation with overall survival in cervical cancer patients are given in Table 2. In addition, the presence of lncRNAs has been demonstrated in exosomes too where they are protected against degradation. The exosomes are known to transport nucleic acids, lipids and proteins from one organelle to another and the transport material varies according to the pathological conditions. In many cancers including prostate, breast and cervical cancer, exosomal lncRNAs have been found to be differentially expressed which makes them excellent choice for biomarkers [136, 146, 147, 155]. It is an active research area promising minimally invasive and dependable biomarkers.

Table 2 LncRNAs as potential biomarkers in cervical cancer

LncRNAs	Type of biomarker	Correlation with overall survival	References
HOTAIR	Prognosis	-	[148]
PVT1	Prognosis	-	[27, 148]
MEG3	Diagnosis and Prognosis	+	[110]
CASC11	Diagnosis	-	[74]
GIHCG	Diagnosis	-	[149]
SNHG14	Prognosis	-	[150]
GHET1	Prognosis	-	[151]
SOX21-AS1	Prognosis	-	[152]
AFAP1-AS1	Prognosis	-	[153]
GAS5	Prognosis	+	[113, 154]
DLX6-AS1	Diagnosis and Prognosis	-	[155]

Potential role in molecular therapeutic approaches

LncRNAs are also being explored for their therapeutic potential. But their role in therapeutics is not discussed prominently due to lack of validation in the clinical studies. Many important signaling pathways like PI3K/AKT (Phosphoinositide 3-kinase/ Protein kinase B), MAPK (Mitogen activated protein kinase), STAT3 (Signal transducer and activator of transcription 3), Wnt/β-Catenin and Notch are reported to be frequently dysregulated by lncRNAs and can provide clinical insight in the management of cervical cancer. The cross-talk of the different signaling cascades and the lncRNAs in cervical cancer is depicted in Fig. 3. A few

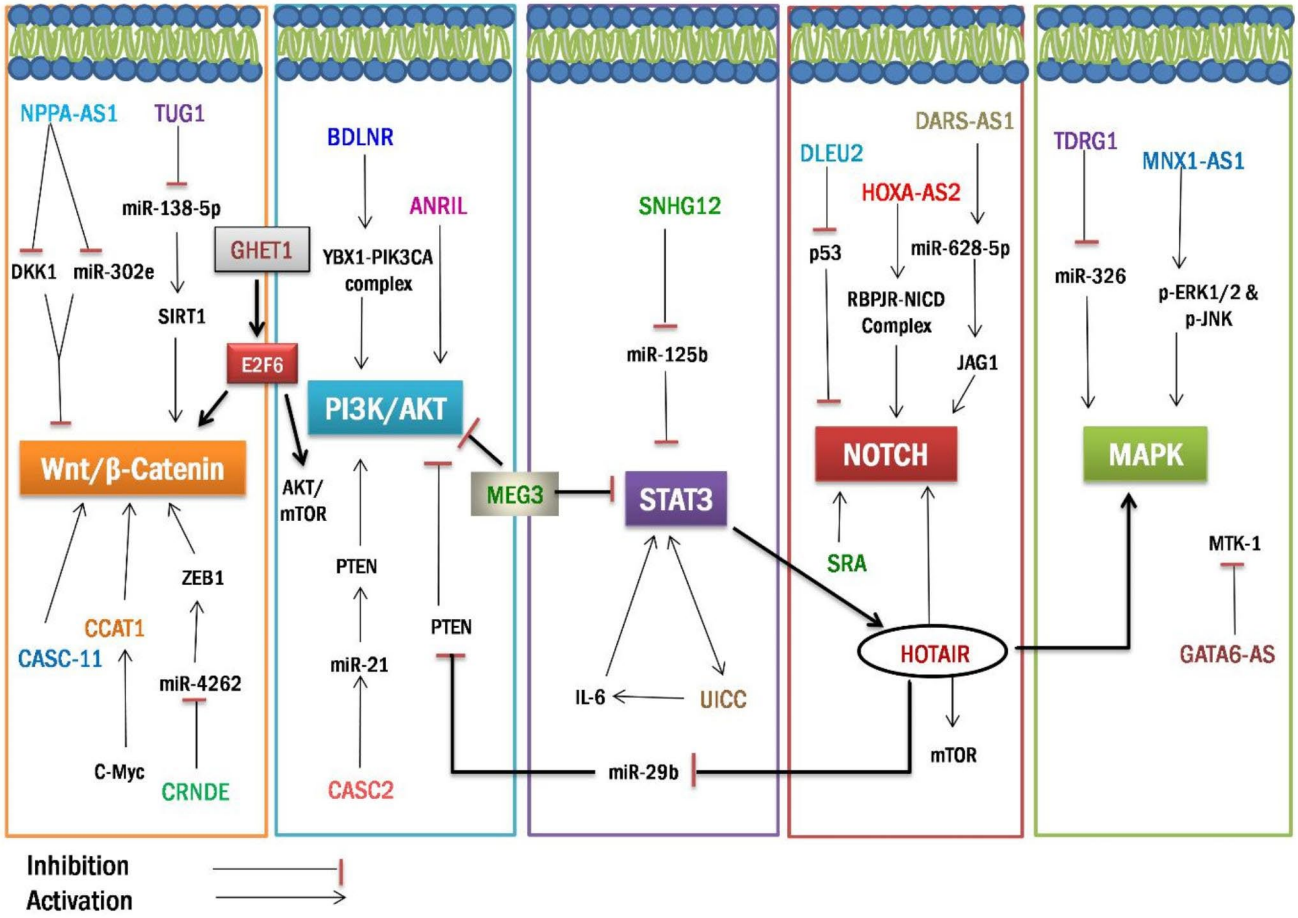

Fig. 3 Crosstalk of lncRNAs with different signaling pathways. Multiple lncRNAs interact with different components of Wnt/ β-Catenin, PI3K/AKT, STAT3, NOTCH and MAPK pathways and contribute to their aberrant functioning to cause cervical cancer

lncRNAs are already under investigation in the clinical management of cervical cancer.

HPV infection is the principal risk factor of cervical cancer and lncRNAs are found to play distinctive roles in HPV induced carcinogenesis. LncRNA CCEPR (Cervical carcinoma expressed PCNA regulatory lncRNA), highly expressed in cervical carcinoma, is positively regulated by E6 oncoprotein [58]. The lncRNA HOTAIR induces the overexpression of another HPV gene E7 which enhances the proliferation and inhibits apoptosis in the cells of the cervix. Other lncRNAs which are regulated by HPV oncoproteins include H19, FAM83H-AS1 (Family with sequence similarity 83 member H antisense RNA 1) and GAS5 [76]. This significant association of HPV oncoproteins and lncRNAs can be manipulated for tackling HPV infection in cervical cancer patients. The involvement of lncRNAs in modulation of intracellular signaling via high risk oncoproteins E6 and E7 is indicated by many researchers but their detailed mechanisms are yet to be uncovered.

The lncRNAs HOTAIR, PVT1 and MALAT1 are related with malignant progression, worse prognosis and chemoresistance along with induced viral replication in cervical cancer. HOTAIR is a trans-acting lncRNA serving in protein ubiquitination, gene silencing via modular scaffolding and recruiting chromatin modulating proteins. It was observed to promote aggressive tumors by regulating VEGF (Vascular endothelial growth factor), MMP-9 (Matrix metallopeptidase 9) and EMT (Epithelial-mesenchymal transition) genes expression. Its role is also elucidated in recruiting PRC2 complex to target DNA sequence leading to trimethylation of H3K27 and further epigenetic silencing of metastatic suppressors [156]. Furthermore, it acts as molecular sponge for a number of miRNAs such as miR-148a, miR-17-5p, miR-203 and functions via different axes viz. miR-143-3P/BCL2 (B-cell lymphoma 2), miR-29b/PTEN (Phosphatase and tensin homolog)/PI3K, HOTAIR/p21 and HOTAIR/HIF-1α (Hypoxia inducible factor-1α) to modulate the expression of their respective targets [23–25, 157–160]. Also, HOTAIR

was found to be upregulated by HPV16 protein E7 while losing the sponge effect against miR-214-3p [161]. Overexpression of HOTAIR was observed to cause aberrant regulation of mTOR (Mammalian target of rapamycin) and Notch pathways and was also associated with lymph node metastasis [162, 163]. To provide a therapeutic insight in this direction, studies were conducted in which Propofol and Artesunate mediated blocking of HOTAIR resulted in marked reversal of tumorous conditions in vivo [162, 164, 165].

MYC (Myelocytomatosis) gene is mostly known to induce tumor hallmarks in the cells and the lncRNA PVT1 co-amplifies with this gene as it is located in its closed proximity. PVT1 shows its oncogenic effects by acting as ceRNA of miR-486-3p to promote cervical cancer cell proliferation [166]. SMAD3 (Small mothers against decapentaplegic) is also well known for its role in oncogenic transformations. Sponging of miR-140-5p is carried out by PVT1 to facilitate invasion through nearby tissues via the upregulation of SMAD3 expression [28]. PVT1 also facilitates the cervical cancer progression by downregulating miR-424 and by sponging miR-503 to upregulate ARL2 (ADP-ribosylation factor-like protein 2) [26, 29]. It has been shown to promote silencing of miR-200b and miR-195 to induce chemoresistance and modulate EMT either by direct sponging or by increasing H3K27me3 modification at the promoter region [167]. Moreover, PVT1 supports the growth of cervical cancer cells irrespective of HPV infection status by deregulating TGF-β1 (Transforming growth factor beta 1) and NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells) pathways [27, 168].

In the cells infected with high risk HPV-16/18, oncoproteins E6 and E7 maintains the tumor phenotype by targeting important tumor suppressor cellular proteins, such as pRB and p53, to modulate the signaling pathways. HPV-16 E7 oncoprotein was earlier believed to cause degradation of these cellular proteins by binding to them. The lncRNA MALAT1 was found to be overexpressed in HPV-16/18 infected cervical cells. However, the overexpression of MALAT1 in these cells is regulated by targeting MALAT1 promoter and IL-6 (Interleukin-6)/STAT3 axis independently of retinoblastoma protein pRB [169, 170]. MALAT1/miR-124/GRB2 (Growth factor receptor bound protein 2) might be another probable axis through which it induces proliferation and invasion of high risk HPV positive cells [171]. In these cells, the sponging of miR-485-5p by MALAT1 results in modulation of MAT2A (Methionine adenosyltransferase II alpha) expression that ultimately controls proliferation of HPV-16 positive cells [172]. It can also act as ceRNA for other miRNAs including miR-145 and miR-429 favouring carcinogenic progression [30, 31]. In a study conducted by Wang et al. (2018), MALAT1 was observed to enhance chemoresistance against cisplatin through the activation of PI3K/AKT signaling mechanism. Moreover, the expression of MALAT1 is recognized as an independent prognostic event in cervical cancer with respect to FIGO staging, tumor size and metastasis to lymph node [173]. Also, it was indicated in a recent study that MALAT1/miR-142-3p axis can be disrupted by using Metformin to develop anti-tumor effects in cervical cancer cells, thereby providing mechanistic insight in therapy designing [174].

The expression of lncRNAs, GAS5 and MEG3, was observed to be lost in cervical cancer cells which resulted in the appearance of cancer hallmarks. GAS5 exhibits a strong association with tumor progression and its reduced expression signifies worse clinical outcomes. It is known to act as ceRNA of miR-196a and miR-205 and downregulates their expression to act as a cancer suppressor [111]. Moreover, its tumor suppressing abilities are also reported through miR-21 mediated regulation of STAT3 signaling which induces apoptosis and causes cell cycle arrest at specific stages [112]. The regulation of miR-21 mediated STAT3 signaling through GAS5 has also been implicated in cisplatin resistance [113]. Furthermore, GAS5 sensitizes the cervical cancer cells to radiotherapy through miR-106b/IER3 axis modulation [175]. Interestingly, its anti-sense counterpart GAS5-AS1 (Growth arrest-specific transcript 5-antisense 1) was observed to inhibit cell proliferation and metastasis by enhancing the stability of GAS5 itself [176].

The overexpression of MEG3 promotes G2/M cell cycle arrest to control proliferation and facilitate apoptosis either along with p53 or without it. MEG3 acts as tumor suppressor via its ability to negatively regulate miR-21-5p and through miR-7-5p/STC1 (Stanniocalcin 1) axis [107, 177]. It also promotes ubiquitination mediated degradation of p-STAT3 to bring about controlled cell growth [108]. In addition, the hypermethylation of MEG3 was found to be strongly associated with very poor overall and recurrence-free survival with high distinction capabilities from healthy to CINIII (Cervical intraepithelial neoplasia III) cases; hr-HPV infection positive or negative and metastasis to lymph node [141]. Clinically, the inhibitory effect of Lidocaine can be utilized to modulate MEG3/miR-421/BTG1 (B-cell translocation gene 1) axis which further induces apoptosis and reduces cell proliferation in an effective manner [178].

The other lncRNAs which act as oncogenes and may be the potential therapeutic targets in cervical cancer include UCA1, NEAT1, TUG1 (Taurine Upregulated Gene 1) and LINC00511. The overexpression of these lncRNAs resulted in appearance of cancer hallmarks and was significantly correlated with the short overall survival as well as worst prognosis in patients. They regulate proliferation, metastasis and invasion through different axis and through the suppression of specific miRNAs. UCA1 enhances cell proliferation and

tissue invasion by upregulating KIF20A (Kinesin family member 20 A) expression via miR-204 sponging and via regulation of miR-299-3p expression [32, 33]. Some recent studies have reported UCA1/miR-493-5p/HK2 (Hexokinase 2) axis interplay in the modulation of glycolytic pathway. This interplay also affects radioresistance of cancerous cells and its overexpression leads to enhanced chemoresistance against cisplatin [179]. Exosomal UCA1 assists in differentiation and self-renewal of cervical cancer cells through axis miR-122-5p/SOX2 (SRY-related high mobility group box 2) [34]. NEAT1 was observed to enhance proliferation and nearby tissue invasion in cervical cancer patients through sponging of miR-9-5p and miR-101 [36]. It also plays important roles via different axes viz. NEAT1/miR-133a by targeting SOX4 to facilitate cancer progression [37], miR-193b-3p/CCND1 (Cyclin D1) axis to promote radioresistance [38], and miR-124/NF-κB to regulate migration and invasion [39]. Furthermore, NEAT1 mediated regulation of miR-361/HSP90 (Heat shock protein 90) contributes to EMT and colony formation [180]. LncRNA TUG1 overexpression was observed in cervical cancer cells and the reports suggested its involvement in cancer cell proliferation and metastasis. TUG1 promotes progression of cervix uteri cancer by miR-138-5p/SIRT1 (Sirtuin 1) axis modulation and also by acting as a ceRNA of miR-381-3p to direct MDM2 (Mouse double minute 2 homolog) overexpression.

Table 3 LncRNAs inducing drug resistance in cervical cancer

LncRNA	Resistance against Drug	Axis involved	References
NNT-AS1	Cisplatin	NNT-AS1/miR-186/HMGB1	[182]
OTUD6B-AS1	Cisplatin	OTUD6B-AS1/miR-206/Cyclin D	[183]
HNF1A-AS1	Cisplatin	HNF1A-AS1/miRNA-34B/TUFT1	[184]
HOTAIR	Cisplatin, Paclitaxel, Docetaxel	miR-29b/PTEN/PI3K	[25]
NCK1-AS1	Cisplatin	NCK1-AS1/miR-134-5P/MSH2	[91]
UCA1	Cisplatin	UCA1/Caspase 3/CDK1 and UCA1/Survivin/p21	[35]
PVT1	Cisplatin	PVT1/miR-195	[167]
TUG1	Cisplatin	TUG1/MAPK	[181]
LINC00958	Cisplatin	LINC00958/miR-185-5p/RSF-1	[185]
ZFAS1	Cisplatin	-	[88]
MALAT1	Cisplatin	MALAT1/PI3K/AKT	[173]
LINC00511	Paclitaxel	-	[143]
BCYRN1	Cisplatin	BCYRN1/miR-330-5p/HMGB3	[186]
PCAT6	Cisplatin	PCAT6/miR-543/ZEB1	[187]
DLG1-AS1	Gemcitabine	DLG1-AS1/miR-16-5p/HDGF	[188]
ANXA2P2	Cisplatin	SOX9/ANXA2P2/miR-361-3p	[189]

As a result, it enhances cell viability and ultimately reduces apoptotic events in the cells [42, 43]. TUG1 was observed to foster angiogenesis and proliferation of endothelial cells specifically. Besides these events, TUG1 is also proposed to aberrantly activate MAPK cascade resulting in development of chemosensitivity against cisplatin [181]. The lncRNAs which play considerable roles in inducing resistance against drugs in cervical cancer are enlisted in Table 3.

The silencing of lncRNA LINC00511 induces cell autophagy and apoptosis by RXRA (Retinoid X receptor alpha) transcription factor mediated PLD1 (Phospholipase D1) expression that sensitizes the cells to the drug Paclitaxel [44]. LINC00511 enhances malignant properties like cell proliferation, migration and surrounding tissue invasion mainly by sponging miR-324-5p which leads to enhanced expression of DRAM1 (DNA damage regulated autophagy regulator 1) [45]. Some other lncRNAs have recently been demonstrated to regulate cell autophagy in cervical cancer. The downregulation of lncRNA RP11-381N20.2 was observed in cervical cancer tissues and when overexpressed, RP11-381N20.2 inhibited the autophagy induced by paclitaxel. On combined treatment with paclitaxel, it significantly increased the apoptosis as well as caused notable reduction in the autophagy. Moreover, its expression was also reported to be correlated with the stage and size of the tumor [190]. Highly expressed ROR1-AS1 (Receptor tyrosine kinase-like orphan receptor 1-antisense RNA 1) was observed to enhance the growth as well as autophagy in cervical cancer cells via ROR1-AS1/miR-670-3p/STC2 (Stanniocalcin 2) axis. The opposite effects on the cell growth and autophagy were observed with the silencing of ROR1-AS1 that ultimately inhibited the malignant characteristics of cervical cancer cells [191]. LncRNA IGFBP4 (Insulin-like growth factor binding protein 4) is negatively controlled by c-Myc, which has a remarkable role in the cell autophagy response. It was reported to be upregulated in cervical cancer and also shown to repress autophagy in the HeLa cell line [192]. To construct a signature of autophagy related lncRNAs having the prognostic value in cervical cancer, a study was recently conducted by Feng et al. (2021) using TCGA (The Cancer Genome Atlas) database and further confirmed by GSEA (Gene set enrichment analysis). They reported 10 autophagy-associated lncRNA signature (AC012306.2, AL109976.1, ATP2A1-AS1, ILF3-DT, Z83851.2, STARD7-AS1, AC099343.2, AC008771.1, DBH-AS1, and AC097468.3) which could differentiate the cervical cancer patients into high and low-risk groups and ultimately predict their 5-year survival outcome [193].

A brief summary of lncRNAs regulating important cellular properties in cervical cancer is shown in Fig. 4.

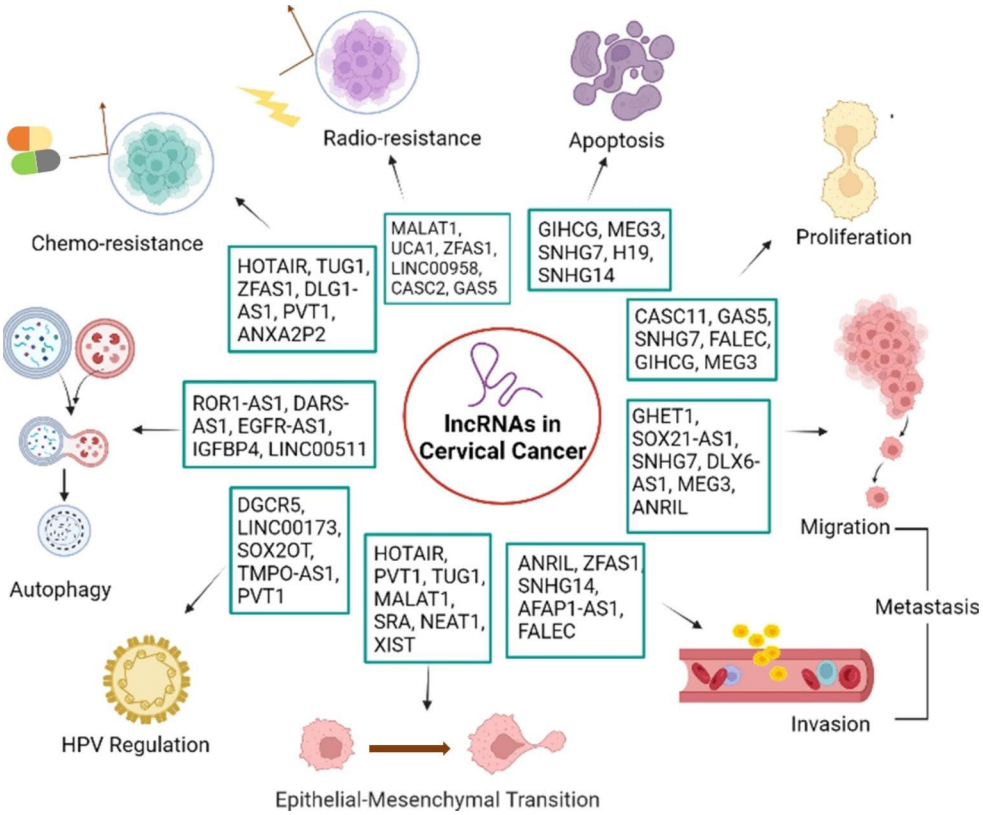

Fig. 4 Brief summary of lncRNAs regulating different cellular properties in cervical cancer

Tools and techniques to study the expanding lncRNA world

In the recent years, the rapid advances in high throughput techniques have uncovered the dynamic and diverse functions of lncRNA. Due to their variable abundance, the tissue specific expression and functional diversity, it has always been challenging to study lncRNAs. For the newly discovered lncRNAs, their localization and functional characterization are crucial to understand their mechanism of action. Certain techniques like lncRNArray, RNA-Seq (RNA-Sequencing), CAGE (Cap analysis of gene expression) and SAGE (Serial analysis of gene expression) are being used for the discovery or the identification of lncRNAs and RNA-FISH (RNA-Fluorescence in situ hybridization), cell fractionation and c-KLAN (Combined knock-down and localization analysis of non-coding RNAs) are used for the localization of lncRNAs [194–196]. To study their primary and secondary structures, techniques including PARS (Parallel analysis of RNA structure), FragSeq (Fragmentation sequencing), PARIS (Psoralen analysis of RNA interaction and structure), SHAPE (Selective 2′-hydroxyl acylation by primer extension) and DMS-Seq (Dimethyl suberimidate sequencing) can be utilized. In order to probe the functional complexity of lncRNAs, loss-of-function and gain-of-function strategies can be used. Successful knockdown of lncRNA can be achieved through the approaches including in vivo loss of function or ASO (Antisense oligonucleotide) and RNAi (RNA interference) mediated depletion [197, 198]. Since the last few years, CRISPR (Clustered regularly interspaced short palindromic repeats) based genome editing has become the most prominent technique to alter the genome in the cell. It has greatly facilitated the inhibition or activation of lncRNA transcription by means of CRISPR interference and CRISPR activation. It involves the Cas9-mediated regulation of transcription and also does not require any manipulation of RNA itself or the RNA locus [199]. The interaction of lncRNAs with other biomolecules can be investigated using techniques like ChIP-PET (Chromatin immunoprecipitation and paired-end tag sequencing), CHART (Capture hybridization analysis of RNA targets) for lncRNA-chromatin interaction; RAP-Seq (RNA antisense purification and sequencing), CLASH (Cross-linking, ligation and sequencing of hybrids) for lncRNA-RNA interaction and RIP (RNA immunoprecipitation), EMSA (Electrophoretic mobility shift assay), filter binding assay, CLIP-Seq (Cross-linking immunoprecipitation sequencing), PAR-CLIP (Photoactivatable ribonucleotide enhanced CLIP) for lncRNA-protein interaction. Some high quality annotation resources are also there for computational identification and characterization of lncRNAs and for the prediction of their relevant associations. LNCipedia provides the information related to the structure, miRNA binding site and the protein coding potential of lncRNAs [200]. The database

lncRNAdb contains the information about structure, nucleotide sequence, sub-cellular localization and gene expression data of lncRNA [201]. For the Pan-cancer and interaction networks, miRNA target prediction, ceRNA and mRNA related information, bioinformatics tools such as starBase, miRCode and lncRNAtor form the relevant resources [197].

Conclusion and future perspective

In the past few years, there have been significant improvements in the area of diagnosis and treatment of locally advanced as well as metastatic cancer of cervix uteri. The therapeutic regimens involving poly-chemotherapy or chemo-radiotherapy have been quite fruitful when compared with monovalent strategies. These treatment strategies are effective if cancer is detected at an early stage and for early detection, routine screening is must. But the uncomfortable diagnostic methods for cervical cancer including Pap test and biopsy test discourage women to undergo routine screening. In addition, cancer cells have a tendency to develop drug resistance over a period of time, rendering the existing therapeutics ineffective. lncRNAs have shown great potential as biomarkers and therapeutic targets in cervical cancer. The differential expression of circulatory lncRNAs in bio-fluids can be explored for the non-invasive detection of cervical cancer. lncRNAs having oncogenic and tumor suppressive role in cervical cancer can be targeted for cervical cancer treatment. Since lncRNAs have also been implicated in drug resistance, the current therapeutic strategies can be combined with specific targeting of lncRNAs to overcome drug resistance.

There are, however, a few limitations which must be addressed before they can be used in clinical practice for cervical cancer treatment. As a biomarker, the major bottlenecks include the variability in gene expression of regional tissue and serum, the collection of quality serum or plasma from the whole blood and the handling of lncRNA quantification [202]. Moreover, for many lncRNAs, it remains to be seen whether the change in their expression is a cause or a consequence of cancer. Also, the absence of any secure and specific delivery vehicle put forward some logical obstacles in their therapeutic application. Other hurdles in their clinical application involve issue of on-target specificity, off-target effects, instability of unmodified and naked structures, and issue of immunogenicity. It is quite evident that many lncRNAs are involved in the pathogenesis as well as progression of cervical cancer but further studies are warranted to help overcome the challenges associated with the clinical applications of lncRNAs.

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Declarations

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