European Review for Medical and Pharmacological Sciences 2019; 23: 3672-3687

Involvement of lncRNA-mediated signaling pathway in the development of cervical cancer

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Abstract. **Cervical cancer (CC) develops, after human papillomavirus (HPV), an infection transmitted through sexual contact. Worldwide estimates are around >500,000 CC diagnoses and >300,000 related deaths annually, and CC remains the second most devastating type of cancers in women after breast cancer. Although the vaccine against HPV has reduced the incidence of infection and the treatment efficacy of the early-stage diagnoses has improved, many challenges remain in terms of treatment efficacy, during the late-stage and prevention of chemotherapy resistance development. Thus, new tools for prompt diagnoses and more effective curative treatments (including the development of targeted gene therapies) are needed.**

The long non-coding RNAs (LncRNAs) (>200 nucleotides) are transcripts that do not encode for any proteins, and they have been linked to the development of cancers (such as leukemia and breast, colorectal, and liver cancers). Some lncRNAs have been identified as the cause of the dysregulation of the oncogenes and progression of CC, but these studies are still very preliminary.

In this review, we explore the literature for lncRNAs involved in the development of CC and their signaling pathways to identify those that might serve as early diagnostic biomarkers, or as targets for gene therapy or other curative treatments.

Key Words

LncRNAs, Cervical cancer, HPV, Markers, Gene therapies.

Introduction

Cervical cancer (CC) is usually caused by high-risk subtypes of the human papillomavirus (HPV) which is mainly transmitted through sexual contact[1]. Each year, more than 500,000 diagnoses and over 300,000 deaths in women are attributed to CC worldwide. In 2018, approximately 311,000 deaths in women were due to CC and, although more than 85% of them were from low-and-middle-income countries, CC remains the second most common cancer affecting women after breast cancer everywhere, even in developed countries[2]. The American Cancer Society estimated 13,170 new diagnoses and more than 4200 deaths from CC in 2019 in USA[3]. In addition, even with the decline in the CC incidence during the last 20 years in developed countries, due to the effectiveness and safety of the HPV vaccine[4] and to the high rates of cure after early diagnosis[3], the persisting high mortality rate is mostly linked to late diagnoses that still represent treatment challenges[3]. Moreover, drug-resistance is another major challenge that also reduces the efficacy of treatments of late diagnosed CC[5].

Thus, new tools for early diagnosis and effective curative therapies are needed. The long non-coding RNAs (lncRNAs), discovered in the 1970s, are a class of about 3000 transcripts longer than 200 nucleotides that do not encode for any proteins[6,7]. LncRNAs may function as decoys, scaffolds, and/or enhancer RNAs, which in turn may interact with, remodel, or regulate the chromatin at the transcriptional and post-transcriptional levels, and may contribute to the development of different diseases[8]. Also, lncRNAs may confer drug-resistance phenotypes[9] and modulate signaling pathways, DNA repair, cell cycle progression, and apoptosis[10]. The aberrant expression patterns of some lncRNAs have been detected in CC cells, precancerous lesions, and in clinicopathological features of CC[11]. In addition, lncRNAs have been shown to act during initiation, development, progression, and metastatic spread of certain malignancies (including breast cancer, colorectal cancer, liver cancer, leukemia, and CC)[8,12,13]. Therefore, lncRNAs may turn out to be effective therapeutic targets and may serve as early diagnostic markers, novel targets for prophylaxis, and/or for effective curative treatment of CC[14].

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We performed a literature review and herein we provide a comprehensive overview of the lncRNAs that have been shown to play a role in CC pathogenesis, and we include the features of their signaling pathways that may lead to the identification of new targets to develop novel diagnostic tools or therapies to cure late-stage CCs.

Papillomavirus (HPV) and Cervical Cancer (CC)

Cervical cancer is caused by the papillomavirus, a double-stranded DNA virus that infects cervix cells[15-18]. More than 100 types and 200 subtypes of HPV have been found, and 14 of them have been identified as high-risk cancer types[19,20], although HPV types 16 and 18 are responsible for 70% of CCs and precancerous lesions[21]. Most HPV infections (~90%) are eliminated by the host immune system. HPV harbours 6 early genes (E1, E2, E3, E4, E5) and two oncoproteins (E6, E7) that regulate viral replication and its interaction with the host cell and two late genes (L1 and L2) that encrypt for the capsid proteins[15,22]. Once inside the host cell, HPV regulates its replication by using the oncoproteins E6 and E7 to integrate its DNA in the host's molecule. Thereafter, the oncoprotein E6 binds the host p53 tumor suppressor gene by inactivating it, whereas the oncoprotein E7 binds to the tumor suppressor genes pRb, p21, and p27, resulting in cell transformation[23]. After this step of entry, the progress of cell transformation from the infection to CC development is slow, through precancerous steps. The process from precancer to CC takes 15 to 20 years in women with normal immune systems and 5 to 10 years for women with weakened immune systems[1]. CC arises when the cervix cells grow abnormally, invading and affecting other tissues and organs (metastasis), including the bladder, vagina, lungs, liver, and rectum[24].

The vaccine against HPV 16 and 18 are very safe and effective in preventing HPV infection[4], but the host environment helps to determine the infection course and the host-virus interactions must be understood in order to design improved therapies.

Origin and Functions of LncRNAs

Back in the 1970s, the non-coding RNA sequences were still considered useless, but this opinion rapidly changed, and the molecules were grouped under the so-called "heterogeneous nuclear RNAs" (hnRNAs). Half of these RNAs were restricted to the nucleus and were transcribed from the repetitive and heterochromatic chromatin regions that contained unknown coding sequences[6,7].

The introns were discovered in 1977[25,26]. This discovery was followed by the official recognition in the 1980s of snRNAs and snoRNAs as the major players in post-transcriptional RNA processing. The evidence for the existence of noncoding transcripts arose in 1992 with the discovery of the lncRNAs involved in the epigenetic regulation, such as Xist[27,28] and H19[29]. However, doubts persisted while the function of most lncRNAs remained unknown. The confirmation of the existence of the importance of lncRNAs and their mechanisms of action gradually emerged with the evidence of their important biological functions as a result of the advances in the sequencing techniques (including transcriptome analysis and bioinformatics prediction technologies)[30-32]. Indeed, the encyclopedia of DNA element (ENCODE) work revealed the low population of RNA transcripts encoding for protein products; for example, only 56 genes showed mass spectrometric evidence of protein expression out of 41,204 (0.1%), highlighting that around 99.9% of RNA transcripts were non-coding[33-37] and suggesting a more diverse role for RNAs in biological processes than previously considered. The data showed that lncRNAs were often overlapped with or interspersed between various multiple coding and non-coding transcripts[38] and their transcriptions were mainly regulated by RNA polymerase II, leaving the transcripts with a 5' terminal cap and being 3' terminal spliced and polyadenylated[39,40].

The non-coding RNAs (ncRNAs) are classified through their size: one group of small RNAs (sRNAs) that are shorter than 200 nucleotides in length (21-24 nt in length) includes microRNAs (miRNA) and Piwi-interacting RNAs (piRNAs)[41], the other group of long RNAs are approximately 200 nt in length or longer and includes the long non-coding RNAs (lncRNAs)[33,42,43].

The lncRNAs have been characterized as signal, decoy, scaffold, guide, or enhancer RNAs, and have been shown to work in conjunction with short functional peptides[44,45]. As RNA decoys, lncRNAs can sequester the regulatory factors by presenting specific binding sites, modulating transcription, and limiting the availability of the regulatory factors (catalytic proteins, transcription factors, miRNAs, subunits of larger chromatin modifying complexes)[46]. In addition, the transcripts from the scaffold class of lncRNAs can structurally act as platforms for the assembly of multiple-component complexes, such as ribonucleoprotein (RNP) complexes[47] that interact with guide lncRNAs directing them at specific target genes or for a proper local-

ization[48]. However, the main function of lncRNAs is to serve as molecular signals to regulate the gene activity in response to various stimuli and particularly to external stimuli and DNA damage[49,50]. The functions of most of the 3000 lncRNAs labeled in humans remain unclear, but they are mostly transcribed by RNA polymerase, and they have been located in different cellular compartments in both cytoplasm and nucleus[51,52] of cells in many tissues. The central nervous system contains the highest diversity of lncRNAs[53] with mostly stable half-lives (over 12 h)[54].

The dysregulation of lncRNAs impacts cellular functions disrupting cell proliferation, induction of angiogenesis, promotion of metastasis, resistance to apoptosis, and evasion of tumor suppressors[43,55-57]. In cancer, for example, lncRNAs work through several ways including in the remodeling and interactions with chromatins, like signals as scaffolds, in transcription regulation through genome enhancers, and in the stabilization and maintenance of chromatin loops[58-64]. LncRNAs can act through chromatin remodeling to achieve transcriptional regulation[65] or can modulate the transcription by sequestering regulatory factors such as catalytic proteins or subunits of larger chromatin-modification complexes and transcription factors[46]. Several lncRNAs also interact with chromosome-modification complexes and direct them to specific target genes as guide lncRNAs, which are essential for the appropriate localization of the chromosome-modification complexes[66].

Since their discovery, lncRNAs have been associated with human diseases, in particular, cancers[67,68] including Leukemia[69,70], glioblastoma[69,71-73], liver cancer[74-76], colorectal cancer[69,77], and CC[78,79]. Some lncRNAs have been used as biomarkers for early diagnosis[80-84] or therapy[85,86].

LncRNAs and Mediated-Signaling Pathways in the Development of Cervical Cancer (CC)

The details of the association between lncRNAs and cervical cancer (CC) are still unclear, as the molecular biogenesis of CC, but the aberrant expressions of lncRNAs have been already identified in CC cells, and it is expected that many of them remain undiscovered.

In our paper, we have focused on 25 lncRNA candidates for diagnostic or/and therapy potentials for CC, classified through alphabetic order including the antisense non-coding RNA in the INK4 locus (ANRIL), the baicalein downregulated lncRNA (BDLNR), the CARD8, the colon cancer-associated transcript 2 (CCAT2), the cervical carcinoma high-expressed1 (CCHE1), the lncRNA-TI17313 (EBIC), the growth arrest-specific transcript 5 (GAS5), the HOX transcript antisense intergenic RNA (HOTAIR), HOXD cluster antisense RNA1, homeobox genes A11-AS (HOXA11), the highly upregulated in liver cancer (HULC), the LINC00473, the long non-coding RNA loc554202 (Loc554202), the metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), the maternally expressed gene (MEG3), the nuclear paraspeckle assembly transcript 1 (NEAT1), the NNT-AS1, the promoter of cyclin-dependent kinase inhibitor 1A antisense DNA damage activated RNA (PANDAR), the plasmacytoma variant translocation1 (PVT1), the Ras suppressor protein 1 pseudogene 2 (RSU1P2), the small nucleolus RNA host gene 1 (SNHG1), the Steroid receptor RNA activator (SRA), the TCONS_00026907, the lncRNA taurine upregulated gene 1 (TUG1), the Urothelial cancer associated 1(UCA1), and the XLOC_010588.

Antisense Non-Coding RNAs in the INK4 Locus (ANRIL)

The antisense non-coding RNA in the INK4 locus lncRNA is transcribed in the opposite direction from its neighboring INK4B/ARF-INK4A gene cluster and was first identified in genetic analysis of a case of melanoma with neural tumors[87]. ANRIL is co-expressed with a genetic marker of coronary artery disease and is upregulated in cases of prostate cancer[87]. In CC, the downregulation of ANRIL includes significant decreases in the expression of the phosphorylated(p)-PI3K and p-Akt. This suggests a contribution of PI3K/Akt pathway in the progression of ANRIL-induced CC. Accordingly, ANRIL knockdown leads to CC cell proliferation and metastasis through the inactivation of the PI3K/Akt pathway[88]. ANRIL has been described as a prognostic biomarker in CC[88].

Baicalein Downregulated LncRNA (BDLNR)

Baicalein downregulated lncRNA (BDLNR) is required for baicalein-induced cell proliferation inhibition, cell death orientation, migration inhibition, and in *in viv*o tumor growth inhibition of CC cells. Baicalein is an active flavonoid extracted from the root of the *Scutellaria baicalensis Georgi* that enhances cell proliferation and migration and induces CC cell apoptosis and cell cycle arrest in a dose-and time-dependent manner. The BDLNR was associated with poor

prognosis in patients with CC. BDLNR recruits YBX1 to the PIK3CA promoter and increases PIK3CA expression by activating the PI3K/AKT pathway[89]. Thus, BDLNR may be a therapeutic target for baicalein for CC treatment.

CARD8

The eQTLs SNP rs7248320 for CARD8 has been associated with an increased risk of CC[90]. CARD8 is a negative regulator of the activation of the nuclear factor Kappa B (NFκB) and suppresses the immune and inflammatory systems[91,92]. NFκB activation signaling contributes to carcinogenesis and promotes disease metastasis in CC[93-95]. This suggests that CARD8 may serve as a susceptibility biomarker for CC[96].

Colon Cancer-Associated Transcript 2 (CCAT2)

Colon cancer-associated transcript 2 (CCAT2) was first discovered in colorectal cancer in 2013[97]. Many studies[97-101] have shown that CCAT2 promotes chromosomal instability, cellular progression, and tumor metastasis in various types of cancers including CC[102], in which its expression is relatively high, compared with that of normal tissues[102], and dependent on the cervical invasion. Of note, the knockdown of CCAT2 inhibits cell development and growth and promotes cell death[103]. The dysregulated activation of the Wnt/β-catenin pathway induced by the transcription factor 7-like 2 (TCF7L2) contributes to the development of human cancers[104].

CCAT2 normally binds to TCF7L2 and upregulates MYC, miR-17-5p, and miR20a expressions triggering the Wnt signaling pathway[105]. However, the upregulation of CCAT2 positively influences the Wnt/β-catenin signaling pathway and promotes the proliferation and the metastasis of cancer cells[106]. In addition, the low levels of CCAT2 have been correlated with metastasis, indicating poor prognosis in CC[107]. Accordingly, the knockdown of CCAT2 induces G0/G1 phase cell cycle arrest and apoptosis[108,109].

Cervical Carcinoma High-Expressed 1 (CCHE1)

Cervical carcinoma high-expressed 1 (CCHE1) is an oncogenic lncRNA overexpressed in CC with significant correlation with the advanced International Federation of Gynecology and Obstetrics (FIGO) stages, increased tumor size, invasion, cervical carcinoma, and poor prognosis. High CCHE1 expression in CC tissues indicates poor recurrence, free survival, and overall survival (OS) of CC patients[110]. CCHE1 binds to and is physically associated with proliferating cell nuclear antigen (PCNA) mRNA, by promoting its expression and consequently increasing proliferation of CC cells. By contrast, the depletion of the proliferating cell nuclear antigen (PCNA) blocks the effects of CCHE1 on the CC cell proliferation. Thus, CCHE1 may be a prognostic factor and therapeutic target in CC[111].

LncRNA-TI17313 (EBIC)

The lncRNA-TI17313 (EBIC) is transcribed from a processed pseudogene located in the chromosome 16q and coded as RP11-144N1.1. The expression of EBIC is higher in CC cells than anywhere else. Physical interaction of EBIC with EZH2 has been reported[112]. EBIC binds to EZH2 and represses E-cadherin, a key molecule for metastasis in CC. This suggested that EBIC may act as an oncogenic lncRNA through the cooperation with EZH2, especially for CC metastasis.

However, the *in vitro* decrease of EBIC expression inhibits CC cell migration and invasion. Additionally, EBIC plays an important role for epigenetic mechanisms in CC cell pathogenesis[112].

Growth Arrest-Specific Transcript 5 (GAS5)

Growth arrest-specific transcript 5 (GAS5) is made of many small nucleolar RNAs namely (snoRNAs), microRNAs (miRNAs), and PIWI-interacting RNAs (piRNAs) located in the 1q25 chromosomal region initially extracted from mouse NIH 3T3 cells by subtraction hybridization[113]. It has been shown that GAS5 downregulation induces tumor suppression in various types of human cancers[114-116] including CC[117,118].

The decrease of GAS5 expression increases the cyclin-dependent kinase 6 (CDK6) expression leading to significant G0/G1 phase shortening and S phase escalation. Thus GAS-5 regulates CDK6[119]. Low GAS5 levels are associated with increased miR-21 and reduced PTEN levels. This last gene product activates the PI3K/Akt pathway, a significant actor in cisplatin-resistant cancer cells[120] and explains cisplatin resistance in cervical cancer cells[118]. Indeed, GAS5 is a tumor suppressor that induces apoptosis and significant suppression of cell growth, tumor invasion, and lymph node metastasis in CC[117]. The signaling P13K/Akt pathway is an important regulator promoting cellular proliferation, cellular growth, and survival. Therefore, GAS5 is an independent marker for predicting the clinical outcome in patients with CC.

HOX Transcript Antisense Intergenic RNA (HOTAIR)

HOX transcript antisense intergenic RNA (HOTAIR) was first identified from the HOXC gene cluster involved in the determination of the proximal-distal axis during development[121-124]. Yet, it has been found in HPV-16-infected CC cells, co-expressed with the oncoprotein E7 of HPV-16, but independently from the viral status. E7 physically and directly interacts with HOTAIR and influences its expression. This may be due to the resulting inability of HOTAIR to bind its targets HOXD10 and HPV-16. Hence, HOTAIR may serve as an early marker for singling out HPV16-positive women[125]. In addition, cell apoptosis by E7 expression and deregulation and the E7 capacity to induce low levels of HOTAIR and high levels of miR-331-3p can be promoted by miR-331-3p. Accordingly, the apoptosis of CC cells is directly regulated by HOTAIR after binding to miR-331-3p[126]. Thus, the suppression of HOTAIR induces a tumor-promoting role to miR-17-5p, thereby providing a new potential strategy for CC treatment.

HOTAIR also selectively interacts with the repressive complex 2 (PRC2), composed by EZH2, SUZ12, and EED[122] to silent the transcription of HOXD locus, resulting in H3K27-trimethylation and gene silencing by histone methyltransferase EZH2[127,128]. In CC, the expression of HOTAIR is associated with molecules VEGF and MMP-9 that play a role in tumor development by increasing cell migration and invasion.

Indeed, high expression of HOTAIR induces upregulation of VEGF and MMP-9, resulting in CC progression. Conversely, the low expression of HOTAIR induces the inhibition of cellular proliferation, migration, and invasion of CC. HOTAIR also reverses epithelial-mesenchymal transition (EMT) by decreasing the expression of E-cadherin while increasing those of β-catenin, Vimentin (VLM), Snail and Twist[129]. EMT plays an important role in cell migration and invasion in CC[64,121,130]. In line with these findings, *in vivo* studies have shown that the knockdown of HOTAIR significantly suppresses the growth and increases the radio-sensitivity of CC through the regulation of genes involved in cell migration and invasion such as VEGF, MMP9, E-cadherin, *VLM,* Snail, Twist and β-cathenin[129]. Additionally, a negative correlation has been observed between HOTAIR and p21, where HOTAIR induces radio-resistance by downregulating the expression of p21[131,132]. Moreover, HOTAIR may promote cellular invasion, migration, and reverse the EMT process[133-135]. HOTAIR is also involved in the recurrence of CC and was found to be correlated with tumor progression, metastasis, and poor prognosis[90,136]. The elevated HOTAIR expression is associated with advanced tumor stages, lymphatic vascular space invasion, adenocarcinoma, and lymphatic node metastasis.

Homeobox Genes A11-AS (HOXA11) LncRNA

The homeobox A11 gene (HOXA11) is expressed in several cancers, and its deregulation (HOXA11-AS) affects CC development, lipid metabolism, alpha-linolenic acid metabolism, drug metabolism-cytochrome P450, malaria, cytokine-cytokine receptor interactions, the MAPK signaling pathway, and arachidonic acid metabolism.

Indeed, the expression of HOXA11-AS is significantly increased in tissues from patients with than in controls. The overexpression of HOXA11-AS has been correlated with poor survival of patients with CC[137]. Although the mechanism affects HOXA11-AS in CC is still unclear, a variety of elements are known to be involved in induced-signaling pathways including a variety of tumor-initiating and progression processes such as cell cycle, DNA replication, oocyte meiosis, and P53 signaling pathway[138].

HOXD Cluster Antisense RNA 1

HOXD cluster antisense RNA 1 (HOXD-AS1) is associated with CC stages, lymphovascular invasion, lymph node metastasis, and recurrence. HOXD-AS1's expression is significantly high in CC cells. HOXD-AS1 knockdown by inactivating the Ras/ERK pathway leads to suppression of CC cell proliferation and colony formation capacity[139]. These data may provide additional information on the pathogenesis, diagnosis, and therapy of CC.

Highly Upregulated in Liver Cancer (HULC) LncRNA

The highly upregulated in liver cancer (HULC) lncRNA was originally discovered in hepatocellular carcinoma cells. HULC is highly expressed in various tumors, such as hepatocellular carcinoma, colorectal carcinoma, osteosarcoma, gastric cancer, and large B-cell lymphoma in which it has been associated with metastasis and prognosis of the respective cancers[140]. In addition, the HULC expression has been associated with the FIGO stages, the presence of lymph nodes metastasis, and cervical invasion. Its overexpression correlates to the overall survival (OS) rates in patients with CC[141].

LINC00473 LncRNA

The LINC00473 lncRNA is increased in CC tissues and plays a role during tumorigenesis. The lncRNA promotes *in vitro* CC cell proliferation and inhibits apoptosis. *In vivo*, LINC00473 enhances CC cell growth. The data[142] have shown that ILF2 degradation is suppressed by the interaction with LINC00473, whereas miR-34a reduces the stability of LINC00473, suggesting that LINC00473 may be a good therapeutic strategy for CC.

Long Non-Coding RNA Loc554202 (Loc554202)

The expression level of the lncRNA loc554202 (Loc554202) is significantly higher in CC tissues and is associated with tumor size, FIGO stage, and lymph node metastasis.

Loc554202 knockdown in HeLa and ME-180 cells inhibit their proliferation ability and induces apoptosis. In addition, Loc554202 decreases Bcl-2 expression and increases Bax expression and appears to be a potential therapeutic target for CC[143]. Loc554202 is an independent prognostic factor for CC, and patients with high levels of Loc554202 have shown lower OSs than patients with low levels.

The Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT 1)

This transcript identified in 2003 in non-small lung cancer (NSCLC) cells is highly expressed in many types of tumors playing roles in the tumor cell proliferation, invasion, apoptosis, and migration[144]. Higher levels of MALAT1 have been found in CC tissue than in normal cervical tissues. High MALAT1 expression seems to lead to splicing malfunctioning[145], and has been associated with poor prognoses. However, another association was found between significantly increased levels of expression of MALAT1 and the presence of HPV infection[78,79]. MALAT1 overexpression in CC has been associated with the stimulation of invasion, tumor growth, and apoptosis inhibition. Conversely, the downregulation of MALAT1 induces the expression of Caspase 3, caspase-8, and Bax, and reduces the levels of Bcl-2 and Bcl-XI, resulting in a reduced migration ability[146-148]. In addition, the depletion of MALAT1 activates the expression of p53 resulting in cell cycle arrest and apoptosis. Interestingly, the proliferation of HeLa cells is suppressed by a MALAT1 inhibitor[126,149]. However, the simultaneous reduction in the expression of cell cycle regulatory molecules like cyclins D1, E, and CDK6 leads to an abundance of cells arrested in G1 phase after the MALAT1 knockdown in CaSki and SiHa cells[79,150,151]. In addition, in radiotherapy, MALAT1 works as a miR sponge resulting in radio-resistance[152]. Finally, MALAT1 is important for the development and progression of CC and may be a good therapeutic target[147,153,154].

Maternally Expressed Gene (MEG3) LncRNA

Initially identified as the human homolog of Gtl2 gene (gene trap locus 2) encrypted on chromosome 12 of a mouse, the maternally expressed gene (MEG3) lncRNA belongs to the DLK1-MEG3 locus imprinted in human chromosome 14q32.3.[155].

Many normal tissues express MEG3, but various mechanisms for the lack of MEG3 expression have been found in cancers including hypermethylation in the MEG3 regulatory regions and IG-DMR, gene eliminations, and even miRNA induced post-transcriptional degradation[156,157]. The transcription factor tumor suppressor 53 (TP53) which arrests the cell cycle and signals apoptosis is closely associated with the development and progression of tumors stimulated by the overexpression of MEG3[158]. The increased MEG33 expression results in the activation of p53 inducing the inhibition of cellular proliferation and apoptosis and suggests a tumor-suppressing role for the lncRNA[159].

Similarly, the activation of the retinoblastoma, another important tumor suppressor involved in cell cycle progression, cell differentiation, and apoptosis, diminishes the expression of DNMT1 and results in the increased MEG3 expression, and ultimately in diminished cell growth[160].

However, the expression level of MEG3 is lower in CC, compared to those in adjacent normal tissues. Likewise, MEG3 expression has been found to be higher in non-neoplastic tissues than in CC tissues; and ectopic expression of MEG3 inhibits the proliferation of HeLa and C-33A cells *in vitro*[161]. MEG3 inhibits CC proliferation via the induction of G2/M arrest and apoptosis[161]. MEG3 suppresses CC through the activation of PI3K/AKT/Bcl-2/Bax/P21 and PI3K/AKT/MMP-2/9 signaling pathways[162]. Thus, the MEG3 expression results in cell growth suppression and apoptosis increase through p53 and caspase. This suggests a tumor suppressor role for MEG3 and a potential target for cancer therapy[161,163].

Nuclear Paraspeckle Assembly Transcript 1 (NEAT1)

Nuclear paraspeckle assembly transcript 1 (NEAT1) expression increases in human cervical tissue and is a predictor of poor clinical characteristics and short survival in patients with CC. In CaSki and HeLa cells, silencing NEAT1 increases the percentage of cells in the S phase and decreases apoptosis. The interaction between NEAT1 and miR-101 suppresses colony formation, cell migration, and invasion suppression, suggesting that NEAT1 promotes CC progression by targeting miR-101[164].

NNT-AS1 LncRNA

The overexpression of NNT-AS1 in CC tissues is positively associated with advanced FIGO stage, lymph node metastasis, depth of cervical invasion, and poor OS. *In vitro*, NNT-AS1 inhibition activates the Wnt/β-catenin signaling pathway and results in inhibited cell proliferation and invasion ability of cells. *In vivo,* silencing NNT-AS1 in nude mice reduces tumor growth. Thus, NNT-AS1 plays a role in cervical carcinogenesis and may serve as a therapeutic target and prognostic marker in the treatment of CC[165].

Promoter of Cyclin-Dependent Kinase Inhibitor 1A Antisense DNA Damage Activated RNA (PANDAR)

The promoter of cyclin-dependent kinase inhibitor 1A antisense DNA damage-activated RNA (PANDAR) is highly expressed in CC patients with shorter survival times than those with lower expression of RNA[166] and is correlated with FIGO staging, tumor size, invasion ability, and survival time in CC. Thus, PANDAR may be a biomarker for the early diagnosis, as well as a therapeutic target in CC patients.

Plasmacytoma Variant Translocation 1 (PVT1) LncRNA

Plasmacytoma variant translocation 1 (PVT1) is an oncogenic lncRNA located in the 8q24 chromosomal region of the human genome, a common site of cancer-related amplifications containing both MYC and PVT1[167,168]. PVT1 overexpression is significantly associated with higher risk, recurrence rates, and poor survival in many cancers[168-173]. PVT1 is frequently co-amplificated with MYC in solid tumors, and overexpressed in CC tissues, correlating with the FIGO stage, tumor size, and poor prognoses. The up-regulation of PVT1 results in the overexpression of miRNAs 1204 and 1206 in CC cells. This demonstrates that PVT1 is associated with proliferation, cell cycle progression, and migration. In addition, miR-424 (a potential target of PVT1) is downregulated in CC tissues. The tumor-suppressive effects induced by PVT1 knockdown may be reverted by the lowered miR-424 expression, suggesting that the transcript may be a novel therapeutic target for CC[174]. Also, PVT1 associates with EZH2 epigenetically silencing miR-200b expression in cervical cancer ensuing cellular proliferation, cell cycle progression, and migration of CC[175]. Accordingly, the knockdown of PVT1 in CC cells decreases cell proliferation, migration, and invasion and increases apoptosis and cisplatin cytotoxicity. This suggests that PVT1 has multiple functions in cervical carcinogenesis[29]. However, PVT1 may be considered a non-invasive diagnostic biomarker for CC, since its levels measured in cervical intraepithelial neoplasia (CIN) and normal cells show that the serum PVT1 is higher in patients with CC than in individuals without it[176].

Small Nucleolus RNA Host Gene 1 (SNHG1) LncRNA

The small nucleolus RNA host gene 1 (SNHG1), is highly expressed in CC tissues and cell lines. In addition, SNHG1 knockdown can decrease cell proliferation, migration, and invasion in HeLa and C33-A cells. However, more evidence needs to be collected before being able to recommend SNHG1 as a biomarker or a therapeutic target[177].

Steroid Receptor RNA Activator (SRA) LncRNA

The steroid receptor RNA activator (SRA) lncRNA is a strong inducer and modulator of gene expression. SRA is related to the EMT and NOTCH signaling pathways *in vitro*. Proliferation, migration, and tumor invasion are suppressed in SRA knockdown CC cell lines[178], suggesting that SRA is a good therapeutic target and prognostic marker for CC.

Urothelial Cancer Associated 1 (UCA1) LncRNA

The urothelial cancer associated 1 (UCA1) gene encodes 3 isoforms and expresses 2 transcripts, including the isoform 2.2 kb in length that has been associated with drug-resistance (CUDR)[179,180]. CUDR has a relative low expression in normal tissues, compared to those of other cancer biomarkers, and this makes it an effective biomarker for cancer development and therapeutic

responses[181]. UCA1 overexpression has been associated with the development of various cancers including CC[179,182]. In CC, UCA1 has been shown to promote cell proliferation, migration, invasion, and cisplatin resistance.

This is due to the activation of the signaling pathways that regulate cell apoptosis involved in balancing the expression of caspase-3, p21, CDK2, and surviving by the lncRNA. Indeed, the increased surviving level and the decreased p21 level boost cellular proliferation and downregulate caspase 3 leading to up-regulation of CDK2 suppressed apoptosis and to cisplatin-resistance in CC cells[181,183]. Therefore, UCA1 may be used as an effective biomarker for therapeutic strategies, as well as for the CC diagnosis[183].

TCONS_00026907 LncRNA

High expression of TCONS_00026907 lncRNA in CC tissues lowers the survival rate of patients. TCONS_00026907 inhibits miR-143-5p, which in turn inhibits ELK1 expression. In HeLa and SiHa cells silencing TCONS_00026907 and ELK1 leads to cell cycle proliferation, migration, and invasion ability suppression, while the overexpression of miR-143-5p promotes apoptosis. This indicates that the TCONS_00026907/miR-143-5p/ELK1 regulatory pathway plays an important role in CC[184].

LncRNA Taurine Upregulated Gene 1 (TUG1)

The expression of lncRNA taurine upregulated gene 1 (TUG1) has been associated with larger tumor size, advanced FIGO stage, poor differentiation, presence of lymph node metastasis, and poor OS. In CC cells, TUG1 is upregulated and promotes tumor processes, and after TUG1 knockdown, cell growth and metastasis are suppressed *in vitro*, and tumor growth is suppressed *in vivo*[185]. CC cell proliferation with the activation of Wnt/β-catenin signaling pathway by SIRT1 activation[186] can be inhibited by TUG1 binding to miR-138-5p and suppressing its expression. Additionally, the knockdown of TUG1 induces cell proliferation suppression and TUG1 silencing leads to the inhibition of cell migration and invasion through the progression of EMT. This suggests that TUG1 is a good therapeutic target[187].

XLOC_010588

The low expression of XLOC_010588 in CC tissues has been correlated with the advanced FIGO stage, compared with the expression in adjacent tissues. OS of XLOC_010588 was considered as an independent predictor for the development and progression of CC. A correlation between the mRNA expression of c-Myc (a regulator of proliferation, growth, differentiation, apoptosis[188], and promotion for many malignant diseases[189]), and that of XLOC_010588 in CC supports the role of XLOC_010588 in c-Myc expression. This suggests that the upregulation of Myc expression is a major event in cancer pathogenesis or progression[190] and that this upregulation is itself regulated by XLOC_010588, suggesting that XLOC_010588 suppresses the expression of c-Myc. Of note, the upregulation of XLOC_010588 in CC cells significantly inhibits DNA replication, while the downregulation of XLOC_010588 significantly promotes DNA replication.

However, XLOC_010588 may bind c-Myc mRNA and decrease its expression by inducing cell cycle arrest and promoting cell proliferation in CC[191]. Thus, XLOC_010588 may be a good therapeutic target for CC.

Conclusions

We have overviewed the role of several investigated lncRNA candidates associated with HPV and CC which may play roles during cell proliferation, migration, tissues invasion, cell survival, promotion of apoptosis, and all-over key pathways involved in the development of CC. Therefore, lncRNAs may serve as prognostic factors or solutions for early diagnosis of CC. Additionally, lncRNAs have been found to be involved in treatment efficacy, individual treatment, and occurrence and progressive mechanisms for CC, suggesting the possibility of being effective targets for CC therapies after both early and late diagnoses. However, the molecular mechanisms uniting lncRNAs, ncRNAs, and mRNAs still need to be clarified. In addition, considering the large amount or lncRNAs, additional studies will probably lead to the discovery of new properties of yet uncharacterized lncRNAs, or to the discovery of additional and better candidates for CC diagnosis, prognosis, and therapies.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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