The Biological Significance of Long noncoding RNAs Dysregulation and their Mechanism of Regulating Signaling Pathways in Cervical Cancer

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Submitted 24 December 2020; Accepted 1 August 2021; Published 1 September 2021

Despite the remarkable decrease in cervical cancer incidence due to the availability of the HPV vaccine and implementation of screening programs for early detection in developed countries, this cancer remains a major health problem globally, especially in developing countries where most of the cases and mortality occur. Therefore, more understanding of molecular mechanisms of cervical cancer development might lead to the discovery of more effective diagnosis and treatment options. Research on long noncoding RNAs (lncRNAs) demonstrates the important roles of these molecules in many physiological processes and diseases, especially cancer. In the present review, we discussed the significance of lncRNAs altered expression in cervical cancer, highlighting their roles in regulating highly conserved signaling pathways, such as mitogen-activated protein kinase (MAPK), Wnt/β-catenin, Notch, and phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathways and their association with the progression of cervical cancer in order to bring more insight and understanding of this disease and their potential implications in cancer diagnosis and therapy.

Key words: Cervical cancer, human papillomavirus, long noncoding RNA, signaling pathways, gene regulation

Worldwide, cervical cancer (CC) is a major public health issue, ranking the fourth most diagnosed cancer, and the second leading cause of cancer-related deaths in women (1). Clinical and
epidemiological shreds of evidence reported that the occurrence of CC requires a prior persistent infection with human papillomavirus (HPV) (2). However, HPV infection alone is not sufficient and other cofactors including host genetic alterations and epigenetic modifications are needed for the progression from benign lesions to malignant tumors (3). The lack of accurate understanding of host factors and genetic background of this disease might explain the failure of current treatment options leading to high mortality rates.

The sequencing of the complete human genome by the human genome project in 2003 promised to offer more insights to our understanding of human physiology and resolving human genetic diseases including cancer (4). Thus, the encyclopedia of DNA elements (ENCODE) project that took over after human genome project completion, deciphered the obtained sequences and provided more in-depth data and analyzed the regulatory elements within the genome (5). Among the biggest discoveries of ENCODE is that the non-coding part of the genome which was described as junk DNA is mostly transcribed into functional RNA molecules, named non-coding RNAs (ncRNAs) (6). This part of the genome is not fully characterized despite the numerous studies on ncRNAs, providing an enormous field of genomics that is yet to be explored.

Several hypotheses are suggested regarding the role of ncRNAs, but their role in gene regulation is well discussed as they influence gene expression without DNA sequence alterations (7). ncRNAs are divided into 2 subclasses according to the length of the RNA molecule: small ncRNA (sncRNA) (20–200 nucleotides) and long ncRNA (lncRNA) (more than 200 nucleotides). Emerging findings report that lncRNAs, with tissue-specific expression, are involved in diverse cellular and physiological pathways including cell differentiation, maintaining cellular homeostasis, regulation of the immune response to disease, differentiation, and DNA damage repair (8,9). During malignancy, aberrant expression of lncRNAs is reported in many cancers, suggesting their role in the modulation of the physiological and molecular changes occurring in the transformed cells (9). Evidence from previous researches indicates that lncRNAs mainly interact with proteins, RNA, and DNA and function at transcriptional, translational, and post-translational levels (10). Moreover, Khalil et al. have reported that more than 20% of lncRNAs bind to the polycomb repressive complex 2 (PRC2) and other chromatin modifiers suggesting that chromatin modification might be a common mechanism of lncRNAs action (11).

In cervical cancer, an increasing number of functional studies have reported that dysregulation of the expression of diverse lncRNAs is involved in the regulation of malignant progression. In fact, the abnormal expression patterns of lncRNAs often correlate with the development and progression of cancer and play a crucial role in cell proliferation, invasion, and metastasis (12–14). lncRNAs exert their functions in CC mainly through the regulation of gene expression, which appears to be mediated by different processes such as chromatin state modulation and RNA processing (15). In CC, a number of lncRNAs showed abnormal expressions, such as HOX antisense intergenic RNA (HOTAIR), plasmacytoma variant translocation 1 (PVT1), and growth arrest specific 5 (GAS5), which are associated with disease progression and poor prognosis (16–18). On another hand, growing interest is given to the role of lncRNAs in viral replication and pathogenesis supporting the involvement in the host-pathogen interaction and suggesting the initiation and promotion of associated diseases (19,20). In the present review, we discuss the significance of lncRNAs altered expression in CC, highlighting their roles in regulating highly conserved signaling pathways, such as mitogen-activated protein kinase (MAPK),...
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Wnt/β-catenin, Notch, and phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathways and their association with the progression of CC.

The implication of lncRNAs in cancer progression

Up to now, many lncRNAs have been reported in CC and are involved in cell proliferation, cell cycle, apoptosis, epithelial to mesenchymal transition (EMT), migration, and/or invasion, such as GAS5, HOTAIR, metastasis associated lung adenocarcinoma transcript 1 (MALAT1), small nucleolar RNA host gene 8 (SNHG8), long intergenic non-protein coding RNA 511 (LINC00511) and MAGI2 antisense RNA 3 (MAGI2-AS3) that were also widely considered as specific biomarkers for early diagnosis (21–26). Studies on the different mechanisms and interactions of lncRNAs with other genes and proteins that confirm the involvement of lncRNAs in CC development and progression are summarized in Table 1.

Almost all of the lncRNAs studied in CC interfere with cell proliferation through direct or indirect interaction with cell cycle proteins and apoptosis pathways. Highly expressed C5orf66 antisense (C5orf66-AS1) in CC was reported to decrease the number of cells in the G1/G0 phase while increasing cell numbers in the G2/S phase. Moreover, overexpression of C5orf66AS1 promoted the proliferation and affected apoptosis and cell cycle through adsorbing the regulator miR-637 (13). LncRNA NCK1-antisense 1 (NCK1-AS1) has been reported to promote cell proliferation and to induce cell cycle progression in CC by interacting with miR-6857 and affecting the cyclin-dependent kinase 1 pathway. NCK1-AS1 induced elevated expression of cyclin dependent kinase (CDK1/6) by antagonizing miR-6857 and led to the control of the G1-S transition in CC cell lines (43,44).

Initially, MAGI2-AS3 was reported to have tumor suppressive activities. However, Liu et al. have found that MAGI2-AS3 up-regulated CDK6 and enhanced cell proliferation in CC (24). This oncogenic trait has been reported in other recent studies confirming that MAGI2-AS3 promotes other cancers types such as colorectal and gastric cancers (45,46). On the other hand, GAS5 was reported as a tumor suppressor lncRNA. Its ectopic overexpression induced cell cycle arrest at G2/M checkpoint which is mediated by the inhibition of cyclin B1 and CDK1 expression by GAS5. Elevated expression of BAX and suppression of BCL-2 is also a consequence of GAS5 overexpression, which ultimately induces apoptosis (22).

LncRNA MALAT1 was previously reported to be highly expressed in CC cells, and was correlated with cancer progression and metastasis (47). MALAT1 is over-expressed in CC, and regulates the expression of apoptosis-related genes such as caspase-3 and 8, BAX, BCL-2, and BCLxL (48). Recent data suggest that HPV E6/E7 and IL-6/STAT3 signaling pathways work synergistically to up-regulate the transcription of MALAT1 in CC HeLa cells, suggesting the cooperation of the virus oncoproteins with cellular inflammatory signaling in CC development (49).

In vitro studies on CC cell lines, showed that HOTAIR plays a role in apoptosis as its knockdown decreased protein levels of anti-apoptotic BCL-2, while it increased protein levels of pro-apoptotic BAX, apoptotic protease activating factor (APAF), caspase-3, caspase-9, and poly ADP-ribose polymerase (PARP) (26). SNHG8, another oncogenic lncRNA, promotes cell proliferation and inhibits apoptosis by recruiting enhancer of zeste homolog 2 (EZH2) to induce the trimethylation of reversion inducing cysteine rich protein with kazal motifs (RECK) promoter and thus inhibiting its expression (23). In addition, LINC00511 recruits transcription factor retinoid X receptor alpha (RXRA) to upregulate the expression of phospholipase D1 (PLD1), and its knockdown promotes autophagy and apoptosis (21).
| LncRNA | Expression level | Interaction with | Mechanism | Biological process | Ref. |
|--------|------------------|------------------|-----------|-------------------|-----|
| MALAT1 | Up               | EMT genes        | MALAT1 up-regulated Transcription factor snail and levels of β-catenin and Vimentin while downregulated E-cadherin and ZO-1 | Invasion and Migration | (25) |
| MAGI2-AS3 | Up               | CDK6             | MAGI2-AS3 up-regulated CDK6 | Cell proliferation and cell cycle | (24) |
| HAND2-AS1 | Down             | ROCK1            | HAND2-AS1 inhibited the expression of ROCK1 | Cell proliferation migration and invasion | (27) |
|         | Down             | C16orf74         | HAND2-AS1 recruited transcription factor E2F4 to C16orf74 promoter and suppressed its expression | Cell proliferation, migration and invasion | (28) |
| SOX2OT | Depends on variants | SOX2             | SOX2OT modulated CC progression via the regulation of SOX2 | Cell proliferation migration and invasion | (29) |
| SNHG16 | Up               | SPI1/ PARP9 Axis | SNHG16 recruited SPI1 protein to promote transcription of PARP9 | Cell Proliferation, invasion and Cell Metastasis | (30) |
| TUG1   | Up               | PUM2             | TUG1 enhanced the progression of CC by its interaction with PUM2 | Cell proliferation and migration | (31) |
| MEG3   | Down             | P-STAT3          | MEG3 bound directly to P-STAT3 protein and induced its ubiquitination and degradation. | Cell proliferation, apoptosis | (32) |
| LINC00511 | Up               | RXRA/ PLD1       | LINC00511 enriched RXRA to the promoter region of PLD1 and promoted its expression. | Cell proliferation, Apoptosis and tumor growth | (21) |
| MIR205HG | Up               | - SRSF1 - KRT17  | Lnc-RNA MIR205HG regulated CC progression through KRT17 by binding with SRSF1 | Cell proliferation, apoptosis and Migration | (33) |
| IncOGFRP1 | Up               | EMT and Apoptosis proteins | The depletion of IncOGFRP1 inhibited the expression of β-catenin, Vimentin, N-cadherin, SNAIL, Bcl-2, cyclinA1, CDK2, and PCNA, and promoted the expression of E-cadherin, Bax, p53, and caspase3 | Cell proliferation, Cell cycle apoptosis and migration | (34) |
| GPC3-AS1 | Up               | GPC3             | ELK1 acts as the transcription activator of GPC3- AS1 and GPC3 | Cell proliferation and migration | (35) |
| CRNDE  | Up               | PUMA             | CRNDE binds to PUMA to inhibit its expression. | Cell proliferation, apoptosis and Tumor growth | (36) |
| LINC00052 | Down             | STAT3            | The mRNA and protein expression of STAT3 was downregulated after overexpressing LINC00052 | Cell proliferation, tumor growth, invasion and migration | (37) |
| GAS5   | Down             | Cyclin B1 and CDK1 | GAS5 induced Cell cycle arrest by reducing the expression of Cyclin B1 and CDK1 | Cell proliferation, Cell cycle, Apoptosis, tumor growth, Invasion and migration | (22) |
| SNHG8  | Up               | EZH2 / RECK      | SNHG8 bound to EZH2 and epigenetically inhibited RECK transcription in CC. | Cell proliferation and migration | (23) |
| SNHG12 | Up               | ERK/Slug         | SNHG12 is modulated by human | Tumor growth and | (38) |
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| Lnc-CC3 | Up     | Slug            | Lnc-CC3 increased Slug expression, and reduced the expression of E-cadherin. | Migration and invasion |
|---------|--------|-----------------|--------------------------------------------------------------------------|------------------------|
| ARAP1-AS1 | Up     | c-Myc           | ARAP1-AS1 might interact with PSF to release PTB, which accelerated IRES-driven translation of proto-oncogene c-Myc | Cell proliferation and migration |
| LINP1   | Up     | KLF2 and PRSS8  | LINP1 scaffolded EZH2, LSD1 and DNMT1 to suppress KLF2 and PRSS8          | Cell proliferation and apoptosis |
| LINC02535 | PCBP2   | LINC02535 interacted with PCBP2 to regulate DNA damage repair by stabilizing RRM1 mRNA in CC | Cell proliferation, migration, and invasion |

The role of lncRNAs in epithelial to mesenchymal transition, invasion, and migration

EMT is a cellular biological program that drives the transition of cells between adherent epithelial state to mesenchymal phenotypes. Epithelial cells undergo series of changes to acquire the characteristics of mesenchymal cells such as stemness, motility, invasiveness, and resistance to therapy, leading to an increased ability of transformation and migration to distant organs (50). Several studies have indicated that EMT, invasion, and migration are in part regulated by some lncRNAs. For instance, lncRNA SRY-box transcription factor 2 (SOX2) overlapping transcript (SOX2OT) contributed to cell proliferation, migration and invasion of CC cells via the regulation of -box SOX2 (29). HOTAIR interacted with key genes that regulate cell invasion and metastasis such as STAT3, β-catenin, vascular endothelial growth factor (VEGF), E-cadherin, matrix metalloproteinases (MMP-9), vimentin, snail, and twist, all of which are involved in EMT, invasion, and migration (51). Consistently, Lee et al. (2016) have investigated the expression levels of EMT related genes in vivo and found that β-catenin, N-cadherin, vimentin, snail, and twist were highly expressed in tumors overexpressing HOTAIR in comparison with the controls (26).

LncRNA-CTS may contribute to EMT, migration and invasion in CC cells through TGF-β1. In fact, lncRNA-CTS regulates TGF-β1 via sponging miR-505, which in turn is responsible for the regulation of zinc finger E-box binding homeobox 2 (ZEB2) mRNA (52). ZNF667-AS1 is a tumor suppressor lncRNA that also employs sponging microRNA mechanism to reduce tumor
invasion and metastasis in CC by competitive binding to miR-93-3p, and thus upregulating PEG3 (53).

GAS5-AS1 is another tumor suppressor that inhibits cell proliferation and metastasis of CC both in vitro and in vivo through increasing the expression of another tumor suppressor IncRNA, GAS5. GAS5-AS1 appears to enhance the stability of GAS5, and thus increasing its expression, by reducing its N6-methyladenosine (m6A) modification (54).

Involvement of lncRNAs in signaling pathways

Deregulated expression of lncRNAs is involved in the initiation and promotion of CC development, invasion, and metastasis through their interactions with several signaling pathways. Numerous lncRNAs, comprising among others HOTAIR, MALAT1, GAS5, EMT, and maternally expressed gene 3 (MEG3) are involved in conserved signaling pathways such as Wnt, MAPK, NOTCH, and PI3K/AKT pathways (Table 2). Altogether, they have been shown to be associated with various pathogenic processes such as tumor progression, invasion as well as therapeutic resistance, and have emerged as new diagnostic and prognostic biomarkers in CC (55).

lncRNAs interfere with the Wnt signaling pathway in CC

Wnt/β-catenin is a highly conserved signaling pathway that plays key roles in the development of cancer through modulating cell growth, cell regulation, and cell differentiation. Abnormal activation of the Wnt signaling pathway, which is the result of aberrant genetic and epigenetic regulation of its components, is linked to the progression of various types of cancers, including CC (84). As for every signaling pathway, Wnt pathway requires spatiotemporal regulation to maintain appropriate biological response and to prevent disease.

Several studies indicate that lncRNAs induce malignant behavior in CC by playing important roles in this regulation. For instance, IncRNA colon cancer associated transcript 1 (CCAT-1) promotes cell proliferation through inhibiting apoptosis in CC cells and RP11-480I12.5 induces the EMT of CC through the Wnt/β-catenin pathway (56,60). In addition, IncRNA ASB16 antisense RNA 1 (ASB16-AS1) acts as a sponge of miR-1305 to prevent its inhibitory effect on Wnt2 and enhance cell proliferation, migration, and invasion (65).

HOTAIR is one of the most studied lncRNAs that is overexpressed in several cancers including CC, and is known by its role in modulating chromatin state by scaffolding the three components of the chromatin-modifying complex PRC2: EZH2, SUZ12, and embryonic ectoderm development (EED) and directs them to distant targeted loci, which consequently induces the H3K27 tri-methylation on promoters of specific genes (16)(85). Through a similar mechanism, HOTAIR appears to regulate the Wnt/β-catenin pathway as well. In fact, HOTAIR was found to recruit tet methylcytosine dioxygenase 1 (TET1) to induce methylation in the promoters of negative regulators of the Wnt/β-catenin pathway such as protocadherin 10 (PCDH10), SOX17, adherens junctions associated protein 1 (AJAP1), and MAGI2, to decrease their expression in HeLa cells (66) (Figure 1).

In vitro downregulation of IncRNA cancer susceptibility 11 (CASC11) in HeLa cells, inhibits the activity of Wnt/β-catenin signaling pathway while overexpression of CASC11 in CaSki cells significantly up-regulated the signaling activity, suggesting that CASC11 was involved in the activation of Wnt/β-catenin signaling pathway (63). CALML3 antisense RNA 1 (CALML3-AS1) is another overexpressed lncRNA in CC. The levels of the Wnt/β-catenin pathway-related proteins such as β-catenin, cyclin D1, and c-MYC were observed to be down-regulated due to CALML3-AS1 knockdown in CC cells, suggesting that the activity of Wnt/β-catenin pathway is promoted by
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**CALML3-AS1**, which might be the mechanism by which Wnt is not expressed, cytoplasmic β-

| Pathway                  | LncRNAs involved | Inhibitors            | Ref.             |
|--------------------------|------------------|-----------------------|------------------|
| Wnt/β-catenin pathway    | CCAT1; DANCR; BLACAT1; CALML3-AS1; RP11-480H12.5; SNHG7; PCAT6; CASC11; NNT-AS1; ASB16-AS1 | DGCR5 (56,57,66,67,58–65) |                  |
| PI3K/AKT/mTOR pathway    | CRNDE; RP1-93H18.6; ANRIL; CCAT1; MF12; NEAT1; MIAT | LINC00037 (DGCR5) (68–74)(75) |                  |
| NOTCH pathway            | HOTAIR; SRA      | -                     | (26,76)          |
| NF-κB Pathway            | PVT1; NEAT1      | -                     | (77,78)          |
| MAPK Pathway             | CASC2; MNX1-AS1; TUG1; TDRG1 | -                     | (16,79–82)       |
| JAK/STAT3                | LINC00518        | -                     | (83)             |

ANRIL: antisense non-coding RNA in the INK4 locus; ASB16-AS1: ASB16 antisense RNA 1; BLACAT1: bladder cancer associated transcript 1; CALML3-AS1: CALML3 antisense RNA 1; CASC11: cancer susceptibility 11; CASD2: cancer susceptibility 2; CCAT1: colon cancer associated transcript 1; CRNDE: colorectal neoplasia differentially expressed; DANCR: differentiation antagonizing non-protein coding RNA; DGCR5: DiGeorge syndrome critical region gene 5; HOTAIR: HOX transcript antisense RNA; JAK: janus kinase; LINC00037: long intergenic non-protein coding RNA 37; LINC00518: long intergenic non-protein coding RNA 518; MAPK: mitogen-activated protein kinase; MIF2: melanotransferrin 2; MIAT: myocardial infarction associated transcript; MNX1-AS1: MNX1 antisense RNA 1; NEAT1: nuclear paraspeckle assembly transcript 1; NF-κB: nuclear factor kappa B subunit 1; NNT-AS1: NNT antisense RNA 1; PCAT6: prostate cancer associated transcript 6; PVT1: plasmacytoma variant translocation 1; SNHG7: small nucleolar RNA host gene 7; SRA: steroid receptor RNA activator; STAT3: signal transducer and activator of transcription 3; TDRG1: testis development related 1; TUG1: taurine up-regulated 1.

When Wnt is not expressed, cytoplasmic β-catenin is degraded by a protein complex composed of proteins that include APC, AXIN, and β-TrCP. When Wnt is expressed, β-catenin is stabilized and translocates to the nucleus, where it can activate transcription of target genes.

**Fig. 1. Regulation of the Wnt/β-catenin signaling pathway and MAPK pathway by lncRNAs and the crosstalk between the pathways.** DANC R recruit FRAT1 and FRAT2 to negatively regulate GSK-3, which inhibits the accumulation of β-catenin and its translocation to the nucleus. LncRNA GHET positively regulates PI3K/AKT/mTOR pathway, which in turn targets GSK-3 and regulates Wnt/β-catenin pathway.
Involvement of lncRNAs in the regulation of conserved signaling pathways.

Differentiation antagonizing non-protein coding RNA (DANCR) activates Wnt/β-catenin signaling pathway through positively regulating frequently rearranged in advanced T-cell lymphomas 1 (FRAT1) and FRAT2 expressions which belong to the GSK-3-binding proteins family that inhibit GSK-3-mediated β-catenin phosphorylation and degradation, which allows β-catenin to reach the nucleus to regulate targeted genes expression (57) (Figure 1). Consistently, the findings of this study indicated that induced overexpression of DANCR enhanced the mRNA and protein expression levels of c-MYC and cyclin D1, which are targeted genes of the Wnt/β-catenin signaling pathway while knockdown of DANCR exhibited the opposite effect (57) (Figure 1).

LncRNAs regulation of phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway in CC

PI3K is a member of the lipid kinases family. In the normal state of the cell, various extracellular factors, such as hormones, growth factors, and cytokines send signals to activate PI3K through the interaction with a phosphorylated tyrosine receptor. PI3K downstream cascade generates signals received by its targets, the most important one being the protein kinase B (AKT) that dominates the signal transduction of the PI3K pathway (87). Activation of AKT is a common phenomenon in human cancers leading to the promotion of cell proliferation (88). The entire PI3K/AKT signaling pathway plays key roles in regulating cell physiology and pathology, including apoptosis, cell proliferation, invasion, and metastasis (88). This pathway is abnormally activated in different tumors including CC (89).

Among the many regulators of this pathway, lncRNAs are also involved, adding more complexity to these processes. Decreased
expression of the antisense non-coding RNA in the INK4 locus (ANRIL) inhibits cell proliferation, migration, and invasion in CC. After the inhibition of ANRIL, the PI3K/AKT pathway was found to be inactivated in CC cells, which indicates that ANRIL might regulate CC progression through the PI3K/AKT pathway (70). In addition, overexpressed RP1-93H18.6 is an oncogenic lncRNA, its down-regulation resulted in the inhibition of cell proliferation and EMT in HeLa cells while promoting cell apoptosis via blocking the PI3K/AKT/mTOR signaling pathway (69). Moreover, lncRNA myocardial infarction associated transcript (MIAT) promotes CC and up-regulates PI3K, AKT, and mTOR levels, indicating its ability to activate PI3K/AKT/mTOR signaling pathway (74) (Figure 1).

LncRNA gastric carcinoma proliferation enhancing transcript 1 (GHET1) was found to regulate CC progression through modulating AKT/mTOR and its cross-talk with Wnt/β-catenin pathways (Figure 1) (90). mTOR is one of the downstream targets of the PI3K/AKT axis. The mTOR axis is up-regulated in CC, and is suggested as a therapeutic target for anti-CC drug development. Blocking mTOR has shown a significant effect in treating HPV-related oral cancer and CCs (91). The crosstalk between AKT/mTOR and Wnt/β-catenin has been demonstrated in many studies. In fact, p-AKT could induce the phosphorylation of Wnt protein receptor GSK3β, which as mentioned above, induces the accumulation and nuclear migration of β-catenin, leading to the activation of Wnt/β-catenin pathway (92) (Figure 2). However, the exact mechanism of action of lncRNAs in regulating this crosstalk in CC is not fully elucidated.

LncRNAs and Notch signaling pathway in CC

Notch signaling pathway plays an important role in different cellular processes such as cell proliferation and apoptosis. NOTCH signaling pathway has two main groups of ligands such as delta-like 1, 3, and 4 and jagged 1 and 2. The binding of these ligands to NOTCH receptors, such as NOTCH 1, 2, 3, and 4 induces the activation of the pathway (93). The activation of the pathways triggers NOTCH cleavage and release of activated NOTCH intracellular domain (NICD). NICD is then translocated into the nucleus, where it activates the transcription of its targeted genes, mainly hairy and enhancer of split-1 (HES1), cyclin D1, and c-MYC. Otherwise, NOTCH can initiate the activation of other signaling pathways such as PI3K-AKT (94).

The CROSSTALK between LncRNAs and Notch pathway was found in several solid cancers. For instance, lncRNA MIR22HG inhibits gastric cancer development and progression through its negative interaction with NOTCH2 signaling (95). LncRNA SNHG12 promotes the progression of osteosarcoma by sponging miR-195-5p, thereby up regulating NOTCH2 (96). GHET1 promotes prostate cancer progression through targeting KLF2 which activates the HIF-1α/NOTCH-1 pathway, and MACC1-AS1 drives pancreatic cancer progression through activating PAX8/NOTCH1 signaling (97,98).

In CC, the NOTCH signaling pathway has a controversial role in alternating pro-oncogenic and tumor-suppressive roles (56). In vitro and in vivo studies showed that high levels of HOTAIR induce higher expression of NOTCH1, HES1, and p300 in CC (26). Steroid receptor RNA activator (SRA) is a type of lncRNA which coordinates the functions of various transcription factors. SRA is related to the EMT and NOTCH signaling pathways, through which it induces in vitro tumor proliferation, migration and invasion (76) (Figure 2). These findings suggest that lncRNAs might promote CC through the NOTCH signaling pathway, representing an interesting way to deeply understand the complex role of this pathway in CC and its relation to lncRNAs.

The role of LncRNAs in mitogen-activated protein kinase (MAPK) pathways in
In its activated state, the MAPK phosphorylates its downstream targets in the nucleus and cytosol to regulate gene expression. There are three families of MAP kinases: JNKs (Jun amino-terminal kinases), ERKs (extracellular-signal-regulated kinases), and p38/SAPKs (stress-activated protein kinases). Numerous studies have shown that MAPK pathways play pivotal roles in CC (99), and numerous lncRNAs have been identified as regulators of the MAPK pathways in CC, through which they modulate cell proliferation, EMT, migration, and response to treatment (80–82).

LncRNA CASC2 is reported to be down-regulated in CC, and acts as a tumor suppressor by inhibiting cell proliferation and migration. Overexpression of CASC2 significantly inhibited the level of proteins of the MAPK pathway such as p-JNK and p-ERK1 in vitro, suggesting that CASC2 might inhibit CC progression via negatively regulating the MAPK pathway (81). Jiang et al. demonstrated that testis development related gene 1 (TDRG1) sponged miR-326 to activate MAPK1, also known as ERK2, and thus suggested the miR-326/MAPK1 as a modulator of CC cell proliferation, migration, and invasion (79) (Figure 2).

In another study, lncRNA taurine up-regulated 1 (TUG1) controlled CC sensitivity to cisplatin through the MAPK pathway. TUG1 knockdown inhibited the proliferative rate but accelerated the apoptosis of cisplatin-induced CC cells (82). Both mRNA and protein levels of regulatory factor X7 (RFX7) were down-regulated by the TUG1 knockdown. Indeed, knockdown of RFX7 could inhibit the proliferative rate and colony formation ability of CC cells. After cisplatin induction in CC cells, phosphorylated levels of p38 and JNK increased, whereas ERK1/2 expression decreased (82). TUG1 knockdown could inhibit the proliferative rate and accelerate the apoptosis of CC cells by activating the MAPK pathway (82) (Figure 2). Zhang et al. analyzed the interaction between HOTAIR and STAT3. They identified a binding site for STAT3 in the promoter region of HOTAIR which is a GAS element. The genes containing GAS elements are regulated by STAT3, therefore, HOTAIR might be regulated by STAT3 as well. Moreover, they showed that HOTAIR and STAT3 affect synergically the aggressiveness of CC (100).

Competing endogenous pathway of lncRNAs in CC

It is widely accepted that gene regulation is more complex than previously expected, involving various regulators, enhancers, and/or transcription factors, acting in cis or in trans. Moreover, several studies have demonstrated that gene regulation is also mediated by microRNAs through complex mechanisms by which they interact with multiple networks. Since then, a growing interest was given to these microRNAs and their role in disease development, including cancer, which has been widely discussed and documented (101–103). Recently, several studies have reported that both coding and non-coding RNA molecules can regulate gene expression in cis and in trans by acting as sponges of microRNAs. These molecules, called competing endogenous RNAs (ceRNAs), represent a major group of gene regulators (104).

Intriguing relation is reported between lncRNAs and microRNAs; lncRNAs often act as molecular sponges or decoys to microRNAs and inactivate them. In turn, microRNAs have the ability to degrade lncRNAs. Together, lncRNAs and microRNAs can compete for binding sites on mRNAs (12,105) (Figure 3). Through this crosstalk between different RNA classes, lncRNAs regulate cancer progression and contribute to the regulation of cell proliferation, invasion, and migration in various cancer cells, including CC (12, 72, 73). Table 3 summarizes the main lncRNAs involved in CC development, their targeted microRNAs, and corresponding downstream dysregulated genes (12,105,106).
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Of particular interest, most lncRNAs are up-regulated to sponge microRNAs and control cancer-

downstream target genes.

Table 3. Recent studies on ceRNA mechanism of lncRNAs in cervical cancer and downstream-targeted genes.

| LncRNA       | Expression level | Targeted miRNA | Downstream genes | Reference |
|--------------|-----------------|----------------|------------------|-----------|
| SNHG16       | Up-regulated    | miR-216-5p     | ZEB1             | (107)     |
|              | Up-regulated    | miR-128        | GSPT1 and WNT3A  | (108)     |
| SNHG12       | Up-regulated    | miR-125b       | STAT3            | (109)     |
| NEAT1        | Up-regulated    | miR-133a       | SOX4             | (110)     |
|              | Up-regulated    | miR-124        | NF-κB            | (78)      |
| MEG3         | Down-regulated  | miR-7-5p       | STC1             | (111)     |
| MACC1-AS1    | Up-regulated    | miR-34a        | CDK6             | (112)     |
| C5orf66-AS1  | Up-regulated    | miR-637        | RING1            | (13)      |
| Linc00483    | Up-regulated    | miR-508-3p     | RGS17            | (113)     |
| LINC01133    | Up-regulated    | miR-4784       | AHDC1            | (114)     |
| LINC00152    | Up-regulated    | miR-216-5p     | HOXA1            | (115)     |
| LncRNA799    | Up-regulated    | miR-454-3p     | TBL1XR1          | (116)     |
| LINC01503    | Up-regulated    | miR-342-3p     | FXRD3            | (117)     |
| ZFPM2-AS1    | Up-regulated    | miR-511-3p     | FGFR2            | (118)     |
| MAGI2-AS3    | Down-regulated  | miRNA-233      | EPB41L3          | (119)     |
| MIR210HG     | Up-regulated    | miR-503-5p     | TRAF4            | (120)     |
| LINC00173    | Down-regulated  | miR-182-5p     | FBXW7            | (121)     |
| FENDRR       | Down-regulated  | Mir-15a-5p/miR-15b-5p | TUBA1A | (122)     |
| CDKN2B-AS1   | Up-regulated    | miR-181a-5p    | TGFβ1            | (123)     |
| LINC01128    | Up-regulated    | miR-383-5p     | SFN               | (124)     |
| NNT-AS1      | Up-regulated    | miR-186        | HMGB1            | (125)     |
| PITPN4-AS1   | Up-regulated    | miR-876-5p     | c-MET            | (126)     |
| ZNF667-AS1   | Down-regulated  | miR-93-3p      | PEG3             | (53)      |
| TTN-AS1      | Up-regulated    | miR-573        | E2F3             | (127)     |
| FOXP4-AS1    | Up-regulated    | miR-136-5p     | CBX4             | (128)     |
| CASC9        | Up-regulated    | miR-215        | TWIST2           | (129)     |
| LINC00473    | Up-regulated    | miR-34a        | ILF2             | (130)     |
| TP73-AS1     | Up-regulated    | microRNA-607   | Cyclin D2        | (131)     |
|              | Up-regulated    | microRNA-329-3p | SMAD2    | (132)     |
|              | Up-regulated    | miR-329-3p     | ARF1             | (133)     |
| TUG1         | Up-regulated    | miR-138-5p     | SIRT1            | (134)     |
| DDN-AS1      | Up-regulated    | miR-15a/miR-16 | TCF3             | (135)     |
| EWSAT1       | Up-regulated    | miR-330-5p     | CPEB4            | (136)     |
| LINC00467    | Up-regulated    | miR-107        | KIF23            | (137)     |
| SNHG20       | Up-regulated    | miR-140-5p     | ADAM10           | (138)     |
| ATB          | Up-regulated    | miR-144        | ITGA6            | (139)     |
| PCGEM1       | Up-regulated    | miR-182        | FBXW11           | (140)     |
| CAR10        | Up-regulated    | miR-125b-5p    | PDK1             | (141)     |
| RP11-552M11.4| Up-regulated    | miR-3941       | ATF1             | (142)     |
| GAS5         | Down-regulated  | miR-21         | STAT3            | (143)     |
| WTI-AS       | Down-regulated  | miR-330-5p     | p53              | (144,145) |
|              | Down-regulated  | miR-203a-5p    | FOXN2            | (146)     |
| HOTAIR       | Up-regulated    | miR-148a       | HLA-G             | (147)     |
|              | Up-regulated    | miR-23b        | MAPK1            | (16)      |
| miRNA       | Regulated State | Gene      | Description   | Reference |
|-------------|-----------------|-----------|---------------|-----------|
| miR-143-3p  | Up-regulated    | BCL2      |               | (148)     |
| miR-206     | Up-regulated    | MKL1      |               | (149)     |
| miR-138-5p  | Up-regulated    | SIRT1     |               | (150)     |
| miR-877-5p  | Up-regulated    | ATXN7L3   |               | (151)     |
| miR-299-3p  | Up-regulated    | FGF2      |               | (152)     |
| miR-361-5p  | Up-regulated    | FOXM1     |               | (153)     |
| miR-4429    | Up-regulated    | MBD1      |               | (154)     |
| miR-127-5p  | Up-regulated    | FOXD1     |               | (155)     |
| miR-107     | Up-regulated    | ZHX1      |               | (156)     |
| microRNA-15a| Up-regulated    | MACC1     |               | (157)     |
| miR-143-5p  | Up-regulated    | ELK1      |               | (158)     |
| miR-183     | Up-regulated    | CCNB1     |               | (159)     |
| mir-101-3p  | Up-regulated    | ZEB1      |               | (160)     |
| mir-199b-5p| Up-regulated    | GBP1      |               | (161)     |
| miR-155     | Down-regulated  | Caspase-3 |               | (162)     |
| miR-299-3p  | Up-regulated    | FGF2      |               | (152)     |
| miR-140-5p  | Up-regulated    | SMAD3     |               | (17)      |
| miR-143-3p  | Up-regulated    | SMAD3     |               | (163)     |
| miR-143-3p  | Up-regulated    | ITGA6     |               | (164)     |
| miR-206     | Up-regulated    | YWHAZ     |               | (165)     |
| miR-493-5p  | Up-regulated    | HK2       |               | (166)     |
| miR-96-5p   | Down-regulated  | PTEN      |               | (167)     |
| miR-21      | Down-regulated  | PTEN      |               | (168)     |
| miR-641     | Down-regulated  | PTEN      |               | (169)     |
| miR-106b    | Down-regulated  | PTEN      |               | (170)     |
| miR-19b     | Down-regulated  | MTUS1     |               | (171)     |
| miR-7       | Up-regulated    | VDAC1     |               | (172)     |
| miR-577     | Up-regulated    | RAB14     |               | (173)     |
| miR-143-3p  | Up-regulated    | ZEB1      |               | (174)     |
| miR-329-3p  | Up-regulated    | SMAD2     |               | (132)     |
| miR-329-3p  | Up-regulated    | ARF1      |               | (133)     |
| miR-214     | Up-regulated    | EZH2      |               | (175)     |
| miR-508-3p  | Up-regulated    | RGS17     |               | (113)     |
| miR-760     | Up-regulated    | HDGF      |               | (176)     |
| miR-543     | Up-regulated    | ZEB1      |               | (177)     |
| miR-122e5p  | Up-regulated    | FOXP2     |               | (178)     |
| miR-485     | Up-regulated    | PAK4      |               | (179)     |
| miR-485     | Up-regulated    | JUND      |               | (180)     |
| miR-181a-5p | Up-regulated    | MMP14 and HB-EGF | (181) |
| miR-218     | Up-regulated    | TPDS2     |               | (182)     |
| miR-7       | Up-regulated    | VDAC1     |               | (172)     |
| miR-361-3p  | Up-regulated    | HOXC6     |               | (183)     |
| miR-329-3p  | Up-regulated    | ARF1      |               | (133)     |
| miR-381     | Up-regulated    | HOXA13     |               | (184)     |
| miR-485     | Up-regulated    | YAP1      |               | (185)     |
| miR-3127-5p | Up-regulated    | RPP25     |               | (186)     |
| miR-16-5p   | Up-regulated    | ARPP19     |               | (187)     |
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| Name       | Up-regulated | Down-regulated | miR                    | Factor/Pathway          |
|------------|--------------|----------------|------------------------|-------------------------|
| XIST       |              |                | miR-200a               | FUS (188)               |
|            |              |                | miR-889-3p             | SIXI (189)              |
|            |              |                | MiR-140-5p             | ORC1 (190)              |
| OIP5-AS1   | Up-regulated |                | miR-143-3p             | ROCK1 (191)             |
| LINC00958  | Up-regulated |                | miR- 625- 5p           | LRRC8E (192)            |
|            | Up-regulated |                | miR- 5095              | RRM2 (193)              |
| SNHG4      | Up-regulated |                | miR-148a-3p            | c-MET (194)             |
| RUSC1-AS1  | Up-regulated |                | miR-744                | BCL-2 (195)             |
| NOC2L-4.1  | Up-regulated |                | miR-630                | YAP1 (185)              |
| TINCR      | Up-regulated |                | miR-302                | Cyclin D1 (196)         |
| TDRG1      | Up-regulated |                | miR-326                | MAPK1 (79)              |
|            | Up-regulated |                | miR-330-5p             | ELK1 (197)              |
|            | Up-regulated |                | miR-214-5p             | SOX4 (198)              |

ADAM10: A disintegrin and metalloproteinase 10; AHDC1: AT-hook DNA binding motif containing 1; ARFI: ADP ribosylation factor 1; ARPP19: cAMP regulated phosphoprotein 19; ATB: activated by transforming growth factor-β; ATF1: activating transcription factor 1; ATXNL3: ataxin 7 like 3; BBOX1-AS1: BBOX1 antisense RNA 1; BCL2: B-cell lymphoma 2; C5orf66-AS1: C5orf66 antisense RNA 1; CAR10: caspase recruitment domain family member 10; CASC2: cancer susceptibility 2; CASC9: cancer susceptibility 9; CBX4: chromobox 4; CCAT1: colon cancer associated transcript 1; CCNB1: cyclin B1; CDK6: cyclin dependent kinase 6; CDKN2B-AS1: CDKN2B antisense RNA 1; CPEB4: cytoplasmic polyadenylation element binding protein 4; CRNDE: colorectal neoplasia differentially expressed; DSN1: DSN and PKR1 antisense RNA 1; DLEU1: deleted in lymphocytic leukemia 1; DLG1-AS1: DLG1 antisense RNA 1; DLX6-AS1: DLX6 antisense RNA 1; DSCAM-AS1: DSCAM antisense RNA 1; E2F3: E2F transcription factor 3; ELK1: ETS transcription factor ELK1; EPB41L3: erythrocyte membrane protein band 4.1 like 3; EWSAT1: Ewing sarcoma associated transcript 1; EZH2: enhancer of zeste homolog 2; FBXW11: F-box and WD repeat domain containing 11; FBXW7: F-box and WD repeat domain containing 7; FENDRR: FOXF1 adjacent non-coding developmental regulatory RNA; FGF2: fibroblast growth factor 2; FGF12: fibroblast growth factor receptor 2; FOXD1: forkhead box D1; FOXD2-AS1: FOXD2 adjacent opposite strand RNA 1; FOXM1: forkhead box M1; FOXN2: forkhead box N2; FOXP2: forkhead box P2; FOXP4-AS1: FOXP4 antisense RNA 1; FUS: fused in sarcoma; FXDY3: FXDY domain containing ion transport regulator 3; GNAS: growth arrest specific 5; GBP1: guanylate binding protein 1; GSP1: G1 to S phase transition 1; HOTAIR: HOX transcript antisense RNA; HOX4: HOX-A13; HOXC6: HOX-C6; HULC: hepatocellular carcinoma up-regulated long non-coding RNA; ILF2: interleukin enhancer binding factor 2; ITGAL: integrin subunit alpha 6; JUND: jun D proto-oncogene subunit; KIF23: kinesin family member 23; LINC: long intergenic non-coding RNA; TP73-AS1: TP73 antisense RNA 1; LRRCSF: leucine rich repeat containing 8; RAR5: RAR5 antisense RNA 1; RAC1: RAC1 antisense RNA 1; RALL: RALL antisense RNA 1; RAS: RAS antisense RNA 1; ROCK1: rho associated coiled containing protein kinase 1; RPP25: ribonuclease P and MRP subunit P25; RRM2: ribonucleotide reductase regulatory subunit M2; RUSC1-AS1: RUSC1 antisense RNA 1; SBF2-AS1: SBF2 antisense RNA 1; SCG5: stanniocalcin 1; SAF: sentinel SF family member; SIX1: six oculis homeobox 1; SMAD2: SMAD family member 2; SMAD3: SMAD family member 3; SNHG: small nucleolar RNA host gene; SOX21-AS1: SOX21 antisense RNA 1; SOX4: SRY-box transcription factor 4; SPRY4-IT1: SPRY4 intronic transcript 1; STAT3: signal transducer and activator of transcription 3; STXBP5-AS1: STXBP5 antisense RNA 1; TBL1XR1: TBL1X receptor 1; TCF3: transcription factor 3; TDRG1: tests development related 1; TGFB1: transforming growth factor beta 1; TINCR: TINCR ubiquitin domain containing; TPO-AS1: TPO antisense RNA 1; TP73-AS1: TP73 antisense RNA 1; TPD52: tumor protein D52; TRAF4: TNF receptor associated factor 4; TTN: TTN antisense RNA 1; TUBA1A: tubulin alpha 1a; TUG1: taurine up-regulated 1; TUSC6: tumor suppressor candidate 8; TWIST2: twist family BHLH transcription factor 2; UCA1: urothelial cancer associated 1; VDAC1: voltage dependent anion channel 1; WT1-AS: WT1 antisense RNA 1; XIST: X inactive specific transcript; YAP1: Yes1 associated transcriptional regulator; YWHAE: tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta; ZEB1: zinc finger E-box binding homeobox 1; ZFP212: ZFP212 antisense RNA 1; ZHOU: zinc fingers and homeoboxes 1; ZNF667-AS1: ZNF667 antisense RNA 1;
Fig. 3. Competing endogenous RNAs interaction. There is a reciprocal negative regulation between LncRNAs and microRNAs, to both compete for mRNA binding sites. This competition leads eventually to gene expression and functional regulation.

development and progression. However, some of them are down-regulated and act as tumor suppressors. These include LncRNAs STXBP5-AS1, TUSC8, phosphatase and tensin homolog pseudogene 1 (PTENP1), and CASC2 binding to miR-96-5p, miR-641, miR-106b, and miR-21 respectively, to regulate the expression of PTEN (167–170). And LncRNA miR503HG, WT1-AS, GAS5, FENDRR, LINC00173, MAGI2-AS3, MEG3, and ZNF667-AS1 that bind to miR-155, miR-203a-5p, miR-330-5p, miR-21, MiR-15a-5p/miR-15b-5p, miR-182-5p, miRNA-233, miR-7-5p, and miR-93-3p to regulate the expression of caspase-3, forkhead box N2 (FOXN2), P53, tubulin alpha 1a (TUBA1A), F-box/WD repeat-containing 7 (FBXW7), erythrocyte membrane protein band 4.1 like 3 (EPB41L3), SClT1, and paternally expressed gene (PEG3) that inhibit cell proliferation and induce apoptosis (53, 111, 119, 121, 122, 143, 146, 162).

The regulation of microRNAs by LncRNAs was also investigated for a better understanding of the treatment outcome in patients with CC. For instance, Feng et al. have shown that TNF-α treatment induced overexpression of LncRNA LOC105374902, which acts as a ceRNA for miR-1285-3p to promote the expression of ribosomal protein L14 (RPL14), and thereby promoting the migration, invasion, and EMT of CC cells (199). Overexpression of LncRNA prostate cancer associated transcript 6 (PCAT6) down-regulated the expression of miR-543 in CC cells, thereby enhanced the level of zinc finger E-box-binding homeobox 1 (ZEB1), playing a key role in chemoresistance of CC cells to cisplatin, and consequently promoting cell proliferation and metastasis (177).

**LncRNAs interaction with HPV in CC**

HPV infection is a key event prior to CC development. Since HPV infection interferes with cellular mechanisms to induce aberrant cell proliferation, it was hypothesized that HPV interacts with LncRNAs in CC as well. Several studies demonstrated that LncRNAs are dysregulated in HPV positive cells and tissues (38, 200–203). This dysregulation is mainly mediated by HPV viral oncoproteins E6 and/or E7 (Figure 4).

Yang et al. reported significant change in LncRNAs expression patterns in HPV positive CC cell lines in comparison with HPV negative cells. They also found that these altered LncRNAs interacted with mRNAs that appear to play key roles in key cellular processes such as DNA repair, cell death, response to stimuli among others, all of
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Fig. 4. LncRNAs and their interaction with HPV viral proteins in cervical cancer. A) viral oncoproteins E6 and E7 recruit transcriptional factor c-MYC to induce the expression of lncRNA SNHG12; B) E6 enhances the expression of lncRNA FAM83H-AS1 through a mechanism involving P300; C) E6 and E7 form a regulatory feedback loop with lncRNA TMPOP2, where E6 and E7 inhibit P53 and its inhibitory effect on TMPOP2 expression, and TMPOP2 induces the expression of E6 and E7, to promote CC; D) HPV viral proteins E6 and/or E7 mediate the overexpression of lncRNAs MALAT1, CCEPR, LINC01101 and LINC00277 in CC.

which being involved in HPV related oncogenesis (203). In Barr et al. study, RNA high-throughput sequencing (RNA-seq) analysis indicated that the expression of host lncRNAs was altered in primary human foreskin keratinocytes cells (HEK) after infection with HPV16 E6 oncogene. The study showed that 151 lncRNAs were upregulated and 100 were down-regulated. In addition, altered expression of some lncRNAs was observed between pre-malignant and cancerous cervical cells (200). Of particular interest, they further evaluated the expression of FAM83H-AS1 lncRNA in primary human cervical keratinocytes (HCK) infected with HPV 16 whole-genome and they found higher expression levels of FAM83H-AS1 in comparison with controls (200). FAM83H-AS1 expression was also increased in HPV 16 positive cervical cell lines (CaSki, W12/201402, W12/20863), and decreased in HPV negative CC cell line (C-33A) in comparison with HCK cells (200). They demonstrated in the same study that FAM83H-AS1 upregulation by HPV 16 is mediated specifically by E6 in a mechanism that does not involve its major downstream target p53. Instead, E6 regulates FAM83H-AS1 through p300 (200).

In another study, HPV16 E6 oncogene-induced IncRNA cervical carcinoma expressed PCNA regulatory (CCEPR) expression. Both HFK cells expressing HPV E6/E7 and HPV positive CC cells (CaSki) expressed higher levels of CCEPR, suggesting the involvement of HPV in increasing CCEPR levels in CC. Moreover, CCEPR overexpression induced by HPV16 E6 was reported to occur in a p53 independent manner (204).
Microarray analysis showed that 3626 lncRNAs were aberrantly expressed in HPV positive cervical squamous cell carcinoma samples versus HPV negative normal controls. Among them, 2077 lncRNAs were upregulated and 1549 lncRNAs were downregulated. Further qPCR analysis confirmed the overexpression of SNHG12, MALAT1, HCG11, colorectal neoplasia differentially expressed (CRNDE), and PVT1 (38). Lai et al. showed also that SNHG12 expression is closely linked to the expression of HPV16 E6 or E7; SNHG12 expression was down-regulated in cells not expressing HPV16 E6 or E7 and up-regulated in cells overexpressing HPV16 E6 or E7, suggesting that HPV16 oncoproteins E6 and E7 might regulate the expression of SNHG12 lncRNA through the modulation of c-MYC (38).

In E7-siRNA transfected HeLa cells, microarray analysis showed that the expression of 15387 RNA species was modified in comparison with controls; among them were 731 lncRNAs and 203 lincRNAs indicating that HPV18 E7 is involved in dysregulating of the expression of RNAs. Among the most dysregulated lincRNAs following E7 depletion, LINC01101 and LINC00277 were particularly increased, which was further confirmed by qPCR analysis. In clinical samples of HPV positive CC patients, LINC01101 and LINC00277 expression was decreased in precancerous and cancerous lesions and their reduced expression correlated with high-risk HPV infections including HPV16 and HPV18 (205).

He et al. found that HPV16/18 proteins E6 and E7 promoted the expression of lncRNA thymopoietin pseudogene 2 (TMPOP2) in CC cells in a mechanism involving p53. Precisely, they found that p53 represses the expression of TMPOP2 by direct binding to its promoter. TMPOP2 in turn regulates the expression of HPV16/18 E6/E7 and enhances their mRNA and protein level at a post-transcriptional level, suggesting that HPV16/18 E6/E7 along with lncRNA TMPOP2 form a positive regulatory loop to regulate gene expression in CC in a synergic manner (206).

MALAT1 was significantly overexpressed in high-risk HPV positive CC cells and tissues in comparison with normal controls and promoted cell proliferation and invasion. In addition, knockdown of HPV E6/E7 inhibited MALAT1 expression in CasKi cells. In clinical samples, MALAT1 was expressed in 30% of HPV-positive normal cervical cells and 60% of HPV-positive cervical lesions, while no expression of MALAT1 was identified in HPV-negative normal cervical squamous cells (47).

Controversially, cells transfected with HPV16 E7 expressed lower levels of HOTAIR, which was described in many studies cited above as an oncogene. Lower expressions of neuropilin 2 (NRP2) and P53 as well as a higher level of miR331-3p were also reported in cells transfected with HPV16 E7, which induced cell growth and inhibited apoptosis. Consistently with these findings, normal HPV positive cervical tissues also showed a reduced level of HOTAIR and NRP2 in comparison with HPV negative normal cervical tissues (202). The interaction of IncRNAs with HPV infection has also diagnosis and therapeutic significance. For instance, LncRNA oncogene-induced senescence 1 (OIS1) was down-regulated in tissues and sera from HPV-positive patients with cervical squamous cell carcinoma and no significant differences were observed between HPV-negative patients and healthy controls. Consistently, OIS1 expression levels were lower in HPV-positive cancer cell lines in comparison with that in HPV-negative cancer cell lines, while no significant differences were found between HPV-positive and HPV-negative normal cell lines. In addition, ROC curve analysis demonstrated that OIS1 could potentially be used as a diagnostic marker for HPV positive but not for HPV negative cervical squamous cell carcinoma (207). Interestingly, it was found that damage induced
noncoding (DINO) lncRNA could restore the function of TP53 in CC. The reactivation of TP53 by DINO increases the vulnerability of CC to standard chemotherapeutics as well as biguanide compounds that cause metabolic stress, which suggests that this lncRNA could be used as a therapeutic alternative to the existing unsuccessful approaches (201).

**Conclusion**

The field of research on lncRNAs is growing each day with newly discovered molecules and new roles and mechanisms of already characterized ones; which provides a large variety of potential clinical applications. LncRNAs function either by direct interaction and inhibition of targeted signaling molecules or indirectly by binding other intermediate molecules such as mRNAs, proteins and microRNAs to alter their regulatory functions.

In CC, a number of lncRNAs such as HOXATIR, PVT1, MALAT1, and GAS5, which are associated with disease progression and prognosis, showed abnormal expressions. They are also involved in the regulation of conserved signaling pathways, such as the Wnt/β-catenin, NOTCH, PI3k/AKT and MAPK pathways. In addition, most lncRNAs are up-regulated to sponge microRNAs and promote cancer development and progression, while, some of them are down-regulated and act as tumor suppressors; these include lncRNAs STXBP5-AS1, TUSC8, PTENP1, and CASC2.

Giving the unavailability of effective treatments for most advanced CCs, lncRNAs diversity in terms of roles and mechanisms provides another set of opportunities. However, lncRNAs occupy several cellular localizations and exert their regulatory functions in a wide range of cellular and pathological contexts. A single lncRNA might also possess different binding sites, and can function through different mechanisms depending on the cellular context. Therefore, more thorough studies are needed to identify key binding sites and to uncover their exact mechanism of action in HPV infection and CC progression to provide precise and targeted options for clinical applications. In addition, tissue specificity and the correlation of lncRNA expression to malignant phenotypes and also to viral infection provides a large field of biomarker research. Thus, more studies on the clinical applications of lncRNAs are required for new targeted therapy approaches and biomarker discoveries.

**Acknowledgment**

Authors would like to thank Hassan II University of Casablanca, Faculty of Science and techniques, team members of Virology, Oncology and Medical Biotechnology, and Virology, Microbiology, Quality and Biotechnologies / Ecotoxicology and Biodiversity laboratory; for all their efforts to support us during the writing and editing this review.

**Conflict of Interest**

The authors declare no conflict of interest.

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